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THE STORY OF ASTHENOPIA: IMPORTANT PART PLAYED BY PHILADELPHIA

WHAT OF THE PRESENT AND THE FUTURE?

WALTER B. LANCASTER, M.D.

BOSTON

The term "asthenopia" came into use just one hundred years ago. MacKenzie, in various papers in the journals and in his remarkable textbook, adopted it as the best term to designate a group of symptoms for which he cited nearly a score of synonyms. The common term in English was "weak sightedness" and in German *Gesichtschwäche*. What Demosthenes called *ἀτονία ὀφθαλμῶν* was well known to the Greeks. He wrote:[1]

> Eyes are said to be atonic when they cannot bear to look at whiteness, brightness or redness (fiery things) but on the least excuse close the lids and water, especially when reading. And these differ from running eyes, because running eyes shed tears without any external excitation, but these [the atonic] do not run without some exciting cause. The treatment is ambulatory, walking, running, gymnastic exercises, etc.[2]

MacKenzie's[2] concise definition was as follows:

> That state of vision in which the eyes are unable to sustain continued exercise upon near objects, although the patient, on first viewing objects, generally sees them distinctly, although he can employ his sight for any length of time in viewing distant objects, and although the eyes appear sound.

In 1842, if one's great-grandfather, then living in England, had suffered from asthenopia, what would have been his fate? He would have consulted one of the leading ophthalmic surgeons, perhaps MacKenzie or Lawrence or Adams. The physician, after examining and questioning the patient, would have noted certain facts which he regarded as important. The patient was, say, 18 years old and a student at Oxford, with good general health and a good family history. The eyes showed no signs of inflammation, present or past, and slight photophobia. There was a tendency to frown. Vision was very good for distant objects and was good for near for a short period. In reading, the print soon became blurred. A few months before, shortly after undertaking some special work involving study of old manuscripts, much of the time by candlelight, the patient noticed the blurring of vision. At first it appeared toward the end of the week, after several days of steady use of the eyes. Resting the eyes over the week-end restored the sight. By degrees the blurring came on earlier in the week. A few weeks before, the patient could read for over an hour, but lately the sight failed in a few minutes, so that he found it impossible to study.

Fifth de Schweinitz Lecture, read before the College of Physicians of Philadelphia, Section on Ophthalmology, Nov. 19, 1942.

1. Demosthenes, quoted by Aetius: *Περὶ ὀφθαλμῶν ἀτονίας· Δημοσθένους*, p. 132; cited by Hirschberg, J.: Wörterbruch der Augenheilkunde, Leipzig, Veit & Co., 1887. This passage was translated by Dr. F. B. Lund, former president of the American Surgical Association and a well known Hellenist.

2. MacKenzie, W.: On Asthenopia or Weak-Sightedness, Edinburgh M. & S. J. **60**:70-103, 1843.

Probably no record would be made of ocular discomfort, headache or other symptoms, local or general, except loss of sight, because at that time such symptoms were not regarded as a part of the picture of asthenopia.

The important questions which the physician tried to answer were, What brought on this serious condition, and what should be done about it? He found that the occupation, study of old manuscripts, was the immediate cause. But many students were able to do this work; there must be some underlying cause and some contributing factors. There had been no acute illness to cause debility; no previous attacks of ophthalmia, especially no scrofulous inflammations of the eyes, and no cerebral symptoms (convulsions). The physician therefore fell back on the explanation commonly given in such cases, that the debility behind the ocular weakness was due to masturbation and spermatorrhea.

The prognosis given was the probable development of amblyopia and even amaurosis.

The treatment advised was (1) cauterization of the urethra (to which MacKenzie devoted considerable space in his textbook), (2) giving up of all use of the eyes for near work and (3) operation, which was mentioned as advocated by some surgeons but was not urged. Spectacles were not advised.

Some days later, while the patient was telling a friend about his sad affliction, his friend interrupted him: "I know just such a case. A young woman, a semptress who worked for my aunt, Lady T., became so blind that she could not see to thread her needle or do her sewing. She went to Lenz, the optician, who sold her some glasses, and now she is working as well as ever. You must see the optician at once. I have no doubt he can cure you."

So the patient went to the optician and was sold a pair of convex lenses, with which he found to his amazement that he could read all he wanted without the horrible blurring coming on. He resumed his work at the university with a profound feeling of relief.

A few months later, not having his glasses with him, he started to do some reading and found that he could not see a word! In a panic he went at once to the physician. The latter told him that what had happened was just what was to be expected. Wearing convex lenses inevitably led to just that loss of sight which he had suffered. It was a sure road to amblyopia. He should give up the glasses and take a prolonged rest in the country or, better still, emigrate to Australia or Canada and take up sheep raising or lumbering. His sight might then be restored. And so it was that one's great-grandfather came to America.

In the 1840's, asthenopia was classed with amblyopia and amaurosis. This may seem extraordinary today, because it is recognized that the visual acuity in asthenopia is usually very good and that even many years of asthenopia do not result in impaired visual acuity. Today inability to use the eyes, not on account of failure of vision, but because of discomfort, distress and fatigue, is the essential consideration. In those days the failure of vision, the blurring coming on when the eyes were used for near work, was regarded as the outstanding fact. The discomfort or even pain in the eyes or head was not deemed important. Ophthalmologists concentrated their attention on the fundamental fact that eyes are for seeing and that loss of sight is the thing to be dreaded. Since the patients described could not use their eyes because they could not see the print or the needle and the stitches, they were losing their sight to all practical purposes. Moreover, it was generally believed that in time asthenopia would result in amaurosis.

Some authors thought the seat of the trouble was in the retina: "amblyopia atopica retinae atonia," Plenck, 1777; disease of the retina from excessive employment, Lawrence, 1841; debility of the retina, *Bristol Eye Infirmary Report*. Others

found the seat in the nerves: amblyopia nervosa, Beer, 1817; weakness of sight from fatigue of the nerves, Scarpa, 1816. Others found it in the muscles: muscular amaurosis, Adams, 1841.[3]

The attitude of ophthalmic surgeons one hundred years ago in the matter of wearing convex lenses throws a flood of light on their conception of asthenopia. They believed that wearing convex lenses caused loss of sight and was dangerous. Convex lenses were often obtained by patients from opticians. After wearing them and finding their ability to read, etc., greatly improved, they discovered to their dismay some months later that when they tried to see without the lenses they no longer were able to do so.[4]

MacKenzie [5] showed his point of view by the following case history (or shall I say anecdote?), quoted by Donders and later by Mauthner: A child, the subject of asthenopia, engaged in learning his lessons, complained that he could not see and repeated the complaint so frequently, especially by candlelight, that his grandfather at last said, "Try my glasses!" The child then saw perfectly, and night after night the loan of the glasses was required before his task could be finished. "It would have been better," said MacKenzie, "had weaker glasses been selected, or better still had he been put to bed, and the lesson left till daylight."

"When a tradition once becomes established by the hall-mark of acknowledged authority, it takes more than cold facts to uproot it from men's minds—it takes time." (Nicholson.[6]) I propose this as the theme, or motive, of my lecture, recurring again and again.

MacKenzie could not escape the influence of his predecessors and contemporaries, as was demonstrated by his caution toward ordering convex lenses in the treatment of asthenopia. In several places he showed that he had more than a glimpse of the true nature of the disease.

When discussing the proximate cause, he said:[7] "As pathological anatomy has thrown no light on the seat or nature of asthenopia, we are left altogether to conjecture, respecting its proximate cause." A sound bit of reasoning then followed:

> The eye, in its normal state possesses a power of adjustment, by which it is enabled to bring to focal points on the retina the diverging rays proceeding from near objects, as well as the parallel rays proceeding from objects which are remote. Wherever the change resides, by which the eye is adapted to the vision of near objects, it is plain that the asthenopic eye is not entirely deprived of the power of effecting that change; for on first looking at near objects, the patient sees them perfectly, and continues to do so until the attack comes on. He then loses sight of near objects and become presbyopic. His vision of distant objects continues distinct, but his eye refuses to sustain the effort necessary for bringing the rays of light, arising from objects within a certain distance, to focal points on the retina. *The organ or organs of adjustment, then, are affected in this disease; and are probably the chief seat of the complaint.*

The italics are mine. Also: "One of the strongest proofs that the seat of the disease must be, in part at least, the apparatus of accommodation, is the fact that the employment of convex glasses relieves the symptoms almost as completely as it does those of presbyopia." [8] He said elsewhere that convex glasses serve merely as a palliative, but a palliative of great importance to those who but for their

3. These authors are cited by MacKenzie.[2]

4. It is not so long since ophthalmologists were using a similar argument against prescribing prisms.

5. MacKenzie,[2] p. 99.

6. Nicholson, W.: Historical Sources of Defoe's Journal of the Plague Year, Boston, Stratford Company, 1919.

7. MacKenzie,[2] p. 90.

8. MacKenzie, W.: A Practical Treatise on Diseases of the Eye, ed. 4, London, Longman [and others], 1854, p. 990.

aid could not win their bread. "They seem to have no effect in removing, neither do they appear, in general, to confirm or aggravate the disease, if properly selected."

The chief obstacle to a clear grasp of the nature of asthenopia by MacKenzie was the lack of knowledge of the mechanism of accommodation. His own hypothesis [9] was that

> . . . the iris and cilary processes are antagonists, so that when the pupil contracts, as it always does on our directing our attention to near objects, the ciliary circle expands and the crystalline lens moves forward, and when we look at distant objects the pupil expands and the ciliary circle contracts around the lens, so that the crystalline will again retire towards the retina. This alternate action of the crystalline probably does not exceed one-twentieth of an inch in extent.

Observations on the dead body seemed to confirm this. "Nor is it at all improbable that the contraction of the straight and oblique muscles, which tends both to elongate the axis of the eye, and shorten the radius of curvature of the cornea, aids the advance of the crystalline."

Finally, MacKenzie summed up in these words: "From these remarks on the proximate cause of asthenopia, the unbiased reader will probably be led to conclude that, although part of the phenomena admit of a plausible interpretation, the true nature of the affection remains a problem."

Of more than passing interest is the operative treatment then in vogue for asthenopia. It was based on the prevalent theory that accommodation was accomplished by the action of the extrinsic ocular muscles, a theory even MacKenzie was not disposed to reject altogether. Cures obtained by tenotomy of rectus muscles, which Scarpa said differed little from miracles, were reported. If one tries to understand how the operation worked, one sees that it was not altogether illogical. Tenotomy for strabismus is followed by improved vision. Why? It was natural to assume that the operation altered the refraction. The physicians of the time knew nothing of the effects of use and of disuse on vision. The greater effort required for convergence after the mesial rectus muscle was cut would favor greater accommodation. The enforced rest following the operation would result in immediate temporary relief. Hence the apparent cure. The same operation was done for myopia, the nature of which was not yet understood. Donders philosophized in these words: "History shows that every discovery and certainly every new operation, usually leads to exaggeration. This is the result of an enthusiasm deeply rooted in human nature, and which has also its good side. Without it, truth appears to gain no victory in the domain of science."

It is the converse that I wish to emphasize in this paper. Equally or even more deeply rooted in human nature, and strongly nurtured in all scientific training, is a profound skepticism of all new propositions. The men who should welcome the new truth, since scientists are seekers after truth, have learned to doubt new ideas. This tendency is wholesome and desirable unless it is carried too far, when it leads to a refusal to listen to the prophet of new ideas and to a conviction that anything conflicting with one's own conception of the truth must be false. The influence of Galen is an outstanding example.

It is not surprising, therefore, that it took a long time for ophthalmic surgeons to give up their ideas about the causes of asthenopia and accept the simple truth of the preponderant influence of accommodation. *"When a tradition once becomes established by the hall-mark of acknowledged authority, it takes more than cold facts to uproot it from men's minds—it takes time."*

During the twenty years between MacKenzie and Donders, considerable progress was made in the understanding of physiology. Helmholtz and von Graefe had

9. MacKenzie, W.: London M. Gaz. **13**:631, 1834; Physiology of Vision, London, Longman [and others], 1841, p. 185.

begun their work. Von Graefe's great contribution to the problem of asthenopia was to point out that one type of asthenopia is due to the extrinsic muscles, but not as factors in accommodation, as previous writers on muscular asthenopia had believed. Von Graefe [10] found the function of convergence at fault and attributed the fault to "insufficiency of the interni." Thus fixation as well as focusing was for the first time shown to be a factor in eyestrain.

I come now to the modern era of ophthalmology.

In 1864 Donders [11] published his great work on refraction and accommodation. He stated: "It is a great satisfaction to be able to say that asthenopia need now no longer be an inconvenience to any one. . . . The discovery of the simple fact that asthenopia is dependent on the hypermetropic structure of the eye, pointed out the way it is to be obviated."

Donders' work was indeed a masterpiece and was recognized at once as such. It was in 1865 that the first scientific session of the American Ophthalmological Society was held. (The first meeting, in 1864, was an organization meeting.) First on the program was a report by B. Joy Jeffries,[12] of Boston, on the progress of ophthalmology during the past year. It is not surprising that he devoted considerable space to Donders' "magnificent" volume published in 1864. He said:

> This work has revolutionized the treatment of anomalies of refraction and accommodation as thoroughly as the invention of the ophthalmoscope revolutionized the treatment of internal affections of the globe. It has, almost like the demonstration of a mathematical problem, not only determined the existence, but the treatment of myopia, hypermetropia, asthenopia and astigmatism. Together with the invention of the ophthalmoscope, the results of this work have served to raise our specialty to a much higher grade in medical science.

High praise, certainly, but no exaggeration.

If one wishes to account for the slowness with which the practice of correcting errors of refraction was taken up by ophthalmologists, one may find a reason in some remarks of Jeffries at the meeting mentioned. He quoted from the *Ophthalmic Review* of April 1864, page 90, and stated:

> It has been happily observed of a book that once produced much controversy, the "Vestiges of the Natural History of Creation," that the most conspicuous fact in connection with its history was the discovery of previously unsuspected strata of ignorance in the so-called intelligent and educated classes. In like manner the introduction of the ophthalmoscope into England was the cause of some sufficiently startling revelations of a similar kind. Many of the leading oculists were found to be unconversant with the elementary facts of optics, and were therefore unable to comprehend the principles upon which the instrument was based, or to speak of it without unconsciously falling into error.

Jeffries went on to say that from remarks here and there cropping out in the journals in reference to Donders' book, he feared that there were still deeper "previously unsuspected strata of ignorance among the so-called intelligent and educated" surgeons and even oculists of the day.

A second reason may be found in the fact that the measurement and the correction of errors of refraction were in the hands of the opticians. Thus, MacKenzie [13] gave the following advice: "When a person wishes to be fitted with glasses, the simplest and surest plan is to try a series of them at an optician's shop." And Risley said that as late as 1870 patients at Wills Hospital with aphakia after cataract operations were sent to opticians to have their refractive corrections worked out.

The story of the first case of refraction corrected at the Wills Hospital will bear repetition. A poor needlewoman had been obliged to give up her work on

10. von Graefe: Arch. f. Ophth. (pt. 2) **5**:186, 1859.
11. Donders, F. C.: On the Anomalies of Accommodation and Refraction of the Eye, translated by W. D. Moore, London, New Sydenham Society, 1864.
12. Jeffries, B. J.: Tr. Am. Ophth. Soc. **1**:3, 1865.
13. MacKenzie,[8] p. 915.

account of her eyes. She sought help from the professor of surgery, who was also lecturer on ophthalmology. He treated her with copper sulfate to the conjunctiva. After twenty treatments, she had used up all her savings and, being still unable to work, went in desperation to the Wills Hospital. Fortunately she went after hours and there were no visiting ophthalmologists on duty, and so she saw the resident intern, Dr. Thomas. It was in 1865, and Thomas had heard of Donders' work. He thought this might be a favorable case. There were no trial lenses in the hospital at that time, and so he borrowed a set from the optician and worked out a correction for the patient. The result was completely satisfactory. The woman was able to resume work and soon earned enough to pay the balance of the surgeon's bill.

Dr. Thomas asked for a trial case for the hospital, and his request was granted. The utilization of this equipment was slow. In 1872, eight years after Donders' book was published, refractions were being performed at the rate of only one every two days at the Wills Hospital. Five years later, in 1877, the rate had increased to two a day.

Yet it was during this very period that the foundations of refraction were being solidly laid in Philadelphia. In 1862 Dyer returned to Philadelphia after studying with Donders and Snellen. Judge the type of man he was by the fact that he brought with him Snellen's idea for making charts with test letters subtending 5 minutes of arc at different specified distances and actually had such charts made and put in use in Philadelphia before Snellen himself had them in use in Holland.

It was at the meeting of the American Ophthalmological Society in 1865 that Dyer reported cases of asthenopia in which the patient was definitely neuropathic. For these he had devised the method (called "dyerism") of gradually increasing the use of the eyes, beginning with five minutes or less at a time and steadily increasing the period by definite daily amounts. This method carried out under the powerful influence of Dyer's personality and reputation, with his own supervision, produced striking results.

There were others, in fact a famous group of ophthalmologists, in Philadelphia. Norris had five years of training in Europe under the best auspices and became a famous Philadelphia ophthalmologist. McClure also studied in Europe, and he was one of those born teachers who love their subject and love to pass their knowledge on to others. He had a large following. To him came William Thompson to have his eyes examined, and so profoundly impressed was Thompson by the result in his own case of getting suitable glasses that he determined to devote himself to ophthalmic surgery instead of to general surgery, as he had planned. Thus Thompson was won to ophthalmology and became one of the most outstanding of a group of eminent ophthalmologists in Philadelphia. I know of two other famous ophthalmologists who were won over by the same experience at about this time, one in New York and one in Boston, which shows that there were practitioners in both those cities skilled in refractive work. The men to whom I refer were John F. Weeks, of New York, and Myles Standish, of Boston, both of whom told me personally how deeply they were impressed by the effect of glasses in correcting their refraction. Doubtless there are many similar cases.

Unfortunately, McClure was estopped from teaching by unenlightened trustees.

Although ophthalmologists had seen and recorded the fact that various symptoms not located in the eye had been relieved by correcting errors of refraction, it remained for a neurologist to grasp the importance, significance and widespread applicability of this fact. Weir Mitchell, another of Philadelphia's immortals, had a patient on whom he had exhausted all his skill in vain. He had been treated by several other eminent doctors. His spine had been cauterized. No one had

suggested an examination of the eyes. His major symptoms did not point to the eyes. However, friends suggested that he might have weak eyes, and he consulted Dr. William Thompson. To the surprise of both Thompson and Mitchell the patient experienced the most complete relief. This case produced a profound impression on Weir Mitchell, which was soon reenforced by a second and a third equally extraordinary case. Weir Mitchell was fully convinced, and his powerful influence, supported by that of the leading ophthalmologists of Philadelphia, who shared in the discovery, started one of the most important American contributions to medicine. Credit must be given to another Philadelphia ophthalmologist and writer, Dr. George M. Gould, who used his facile pen to propagandize. Of Gould it may be said in the words quoted from Donders: "History shows that every discovery . . . usually leads to exaggeration. . . . Without it, truth appears to gain no victory in the domain of science."

Some years later, Risley, another of the Philadelphia *eminentes,* began to contribute to the subject of refraction. He was one of those who stressed the importance of small errors. If a small error of refraction can make trouble, obviously failure by a small amount to correct exactly a larger error may be expected to make trouble. I believe this view is an important foundation stone in the science and art of refraction. It has not prevailed without opposition. The reason for the skepticism as to the need of correcting less than 0.50 D. or of measuring the error to 0.12 D. is that a great many patients do perfectly well with a rough approximation to the true, exact correction. I am fond of telling students that in a fair sample case, say that of a clerk or stenographer in the thirties complaining of eyestrain who has never worn glasses and has a moderate compound hypermetropic astigmatism, I can write a hundred different prescriptions for glasses, any one of which will give marked relief. On the other hand, there are not a few cases in which the patient does not get satisfactory relief until the refraction is corrected with great exactness.

Dr. Edward Jackson, then of Philadelphia, was one of those who worked for more exact measurement of refraction. His great contribution at that time was his book "The Measurement of Refraction by the Shadow Test or Retinoscopy.[14]

In the early days, a correction of some of the hypermetropia, without regard for the astigmatism, gave relief to a large number of persons. There were a good many failures. The literature contains many papers written by men who tried to account for these. As an approximate correction of the astigmatism was added, the number of failures was reduced. As the hypermetropia and the astigmatism were both more accurately measured and more skilfully treated, the number of failures was further reduced. As the heterophorias were corrected, still better results were obtained. Recently the failures have been still further reduced by the correction of aniseikonia. Still there are a good many failures. I believe that improvement must be sought in greater exactness of measurement and greater precision in diagnosis, as well as in greater skill in the application of more exact measurement.

To summarize, in the 1840's, asthenopia was looked on as a condition allied to amblyopia and amaurosis. As no pathologic anatomic basis could be found—"the patient couldn't see anything and the doctor couldn't see anything either"—the cause was sought in general conditions favoring debility. The symptom of chief importance was the blurring of vision—the loss of sight for near objects while distant vision was good. At least one shrewd observer (MacKenzie) suspected the

14. Jackson, E.: Am. J. M. Sc. **89**:404, 1885.

accommodation, but not enough was known about the physiology of accommodation to make possible anything more than a guess.

In 1864 Donders [11] published his great work, in which he showed that hypermetropia and accommodation are the essential causative factors in asthenopia and that convex lenses will cure it. Since accommodation played the major role it was of paramount importance to control the accommodation, and this could be done by use of cycloplegics.

By degrees it became apparent that there were other symptoms besides the blurring of vision, namely ocular discomfort and even pain.

As the good news spread among ophthalmologists, they more and more took an interest in measurement of errors of refraction, a branch of practice which had heretofore been left to the optician.

The practice led to better understanding of the problems and so to improved methods of measuring errors of refraction, including astigmatism.

In the 1880's (I am dividing the time into twenty year periods) the knowledge became fairly general that errors of refraction could cause not only the symptoms classically associated with the term asthenopia but widespread symptoms of a nervous character, which had hitherto resisted all methods of treatment but which yielded as if by magic to glasses properly correcting the errors of refraction.

Two additional steps forward were: first, realization that small errors of refraction can cause trouble and, as a corollary, that exact correction is important, and, second, appreciation of the far reaching importance of disturbances of binocular vision due to defects of motility, often called "muscle trouble."

Thus, at the turn of the century—the next twenty year landmark—the diagnosis and treatment of errors of refraction had become crystallized into a fairly definite practice followed by almost all ophthalmologists, comprising: (*a*) use of a cycloplegic; (*b*) retinoscopy; (*c*) test with the trial lenses, based on the selection of that combination of lenses, spherical and cylindric, which give the best visual acuity, and (*d*) measurements of the heterophoria.

Only a few ophthalmologists continued to use the keratometer, and a few used the astigmatic charts described by John Green in the 1860's. Has there been much change in Philadelphia in the last forty years?

Thus one finds a state of affairs such as has often occurred before in the history of medicine or of science in general.

Not long ago, Robertson [15] cited the statement by Nicholson already quoted, *"When a tradition once becomes established by the hall-mark of acknowledged authority, it takes more than cold facts to uproot it in men's minds—it takes time,"* and added, "Most animals, including, perhaps especially, man, are characterized by their frequently blind adherence to their leaders."

Then a prophet appeared and proclaimed the errors that permeated the current belief and practice. He pointed out the truth, showed the correct way of looking at the problems of ocular refraction, and his words fell for the most part on deaf ears. To be sure he was awarded a Nobel prize, but his teachings failed to permeate the teaching and practice of his contemporaries, and in a feeling of frustration and disappointment he gave up ophthalmology (he was a university professor of ophthalmology) and turned to end his days as a professor of mathematics.

The philosopher may speculate on the striking differences in the way different prophets have been received. Thus, Donders was quickly acclaimed and speedily followed by a great multitude. Why did Gullstrand meet with so little recognition? Such cases are not rare, and it is my belief that the explanations are threefold. In the first place, there must be some preparation of the soil. The time

15. Robertson, H. E.: Proc. Staff Meet., Mayo Clin. **17**:465, 1942.

must be ripe. A prophet who is many years ahead of his time is sure to meet little welcome. This would not apply to Gullstrand. In the second place, much, very much, depends on the way the truth is presented. Many a man has felt that his contributions have been overlooked, ignored and unappreciated, which was obviously true, but the fault was in the way they were presented. A third factor of major importance is the weightiness of the authorities whose teaching is challenged.

I have not read Gullstrand's original articles; I am quite sure I could not follow the mathematics; nor could most other ophthalmologists. A writer on ophthalmology must present the fundamental facts in such form that the average ophthalmologist can understand them. This Gullstrand did in his appendix contributed to volume 1 of the American edition of Helmholtz' treatise on physiologic optics.[16] But even this is not enough. The applications and implications must be clearly pointed out and driven home by clinical examples, and this was not done. Gullstrand made the facts plain enough. He said (I have condensed some of the sentences):

> When Helmholtz's original contributions were published on the Dioptrics of the Eye, the characteristic conception of optical imagery that was current at that time assumed that rays of light emanating at a point were reassembled approximately at another point, and that thus a certain point of the image was associated with a definite point of the object. This conception continues to be very widespread at the present time, although it cannot be reconciled with actual facts as now known [page 261]. . . . The laws of optical imagery in the case of an infinitely small object situated on the axis of a centered system provided with an infinitely narrow stop, were well known. But the theory of collinear imagery applied to objects of finite extent [i. e., real objects] and stops with finite apertures [pupil of the eye, for example], which is the basis of the expositions still to be found in modern text-books, constitutes therefore an essentially arbitrary extension of the region of validity of these laws, inasmuch as a system of fictions had to be introduced in place of the real undiscovered laws [page 262]. . . .
>
> The aberration of the eye as ascertained by a study of the precise geometrical magnitudes that determine the form of the caustic surface together with the position, dimensions and form of the narrowest section of the bundle of rays, was found to be so great, and the blur circles on the retina even with the best focusing turned out to be so large that the role in the imagery assigned to the narrowest cross section of the bundle cannot possibly be correct [page 263]. . . . This shows that the light-distribution inside the section of the ray-bundle is of primary importance whereas the dimensions of the section are of secondary importance. In place of the approximate measures of the dimensions of the narrowest cross section as found by series-development, it was all the more necessary to substitute the precise geometrical magnitudes that determine the form of the caustic surface; because it is the section of this surface that controls the distribution of the light within the section of the ray-bundle [page 263]. . . .

Speaking of the theory of imagery as commonly taught, which was based on a system with an infinitely narrow bundle of rays, Gullstrand said: "But since it is physically impossible on account of diffraction effects to produce an optical image by such means, this imagery represents merely an ideal dreamed of in olden times" (page 268).

Speaking of the cardinal points of which so much is made in the explanation of the formation of an image by lens systems, for example the eye, he stated:

> If we insist on sticking to what is actually the case, this method is no longer justifiable, because the laws on which the construction depends are not valid except for the fiction of rays which are inclined at infinitesimal angles, and therefore such constructions often create false notions. Neither the nodal points nor the principal focal planes afford any advantage in showing what actually takes place, and so these ideas also have been cast aside here as so much useless ballast [page 287].

16. Gullstrand, A., in appendix to Helmholtz, H. L.: Helmholtz's Treatise on Physiological Optics, translated from the third German edition by J. P. C. Southall, Menasha, Wis., George Banta Publishing Company, 1924.

He pointed out the importance of the cusp of the caustic surface for imaging minute detail and also of the light distribution inside the section of the ray bundle. In the eye and likewise on the photographic plate, shades of brightness are of more importance than absolute brightness (page 268).

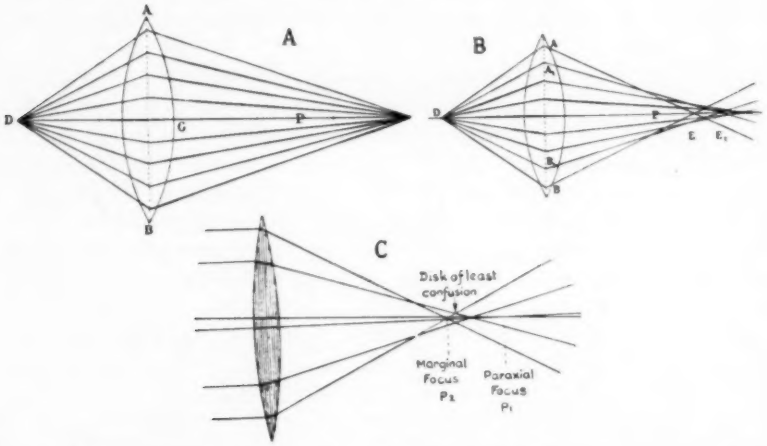

Fig. 1.—*A*, classic diagram, showing how rays from *D* falling on a convex lens all meet at a point focus on the other side. This is purely fictitious. The rays do not meet in a point. *B*, how the rays from the point *D* are actually refracted by the convex lens. Each pair of rays has a different focus from every other pair. *C*, how six rays from a distance and therefore parallel are actually refracted by a convex lens. The two central paraxial rays meet at the paraxial focus P_1. The two most peripheral rays, one above and one below, meet at the marginal focus P_2. The upper marginal ray and the one next to it meet at a point which is not even on the axis.

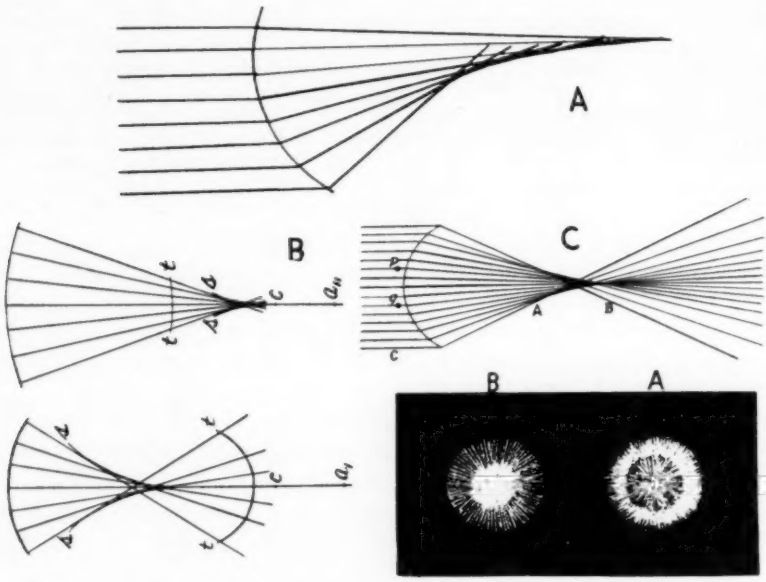

Fig. 2.—*A*, diagram showing how the locus of the various foci forms a caustic surface. In *B*, the heavy lines, *ss*, represent the caustic surfaces in section. If one imagines the three-dimensional appearance one will see that the caustic surface is a lily-shaped surface. *C*, the kind of an image the caustic would give if a screen was placed at *A* and then at *B*. The greatest concentration of light is near the periphery at *A* and in the center at *B*.

Ames and Proctor approached the problem of the formation of an image in the human eye from a different point of view, viz. the experimental. The question they asked themselves was not, What are the mathematical and physical laws governing the behavior of light waves emanating from a point? but the practical question, What form does the image actually take in the eyes of persons actually studied by suitable methods? They made a more elaborate and exact study of the formation of images than any previous investigators. Their findings fitted with Gullstrand's mathematical and experimental observations. They found the magnitude of the aberration to be smaller than Gullstrand calculated. Also, in the 2 persons whom they measured they found that the waist of the ray bundle, that is the narrowest part of the cone, and not some point on the caustic, as Gullstrand stated, was the point chosen for best focus whether the illumination was strong or weak.[17]

The obvious question is, How does all this affect the practice of ophthalmology today? To answer in detail would be a huge undertaking, leading me far beyond

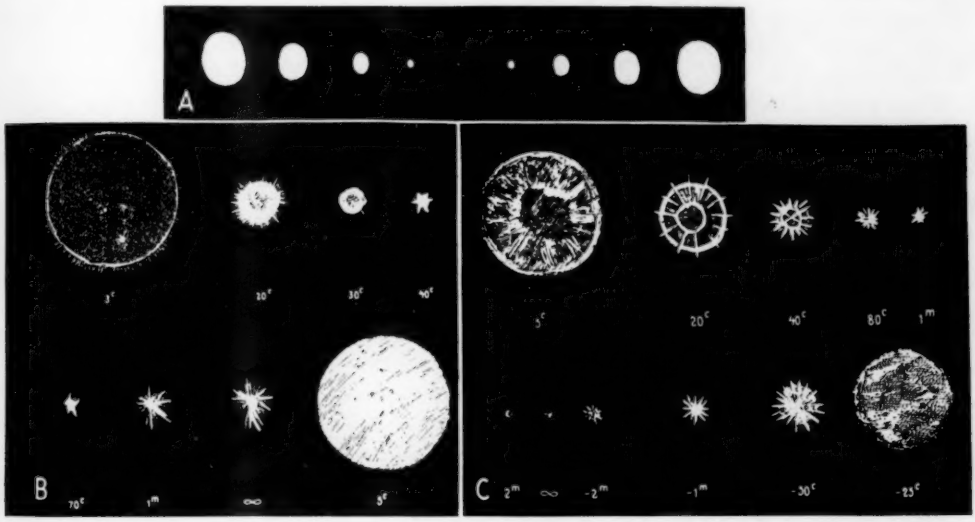

Fig. 3.—According to the classic textbook description, if a screen is placed at the proper distance back of a convex lens and perpendicular to its axis the focus will be a point, and if the aperture of the lens is circular, when the screen is placed at different distances in front or back of the focus the various blur circles will be homogeneous disks, the light equally distributed throughout each disk, as shown in *A*. The white spots should be circular instead of slightly oval, as drawn. This is purely ideal as far as eyes or ordinary ophthalmic lenses are concerned. *B* and *C* show the "blur circles" as they actually appeared to a certain observer, who drew them as they looked to him when the retina intersected the beam at different points. Such intersection is accomplished by changing the distance of the point source in space or by shifting its optical distance by plus or minus lenses. The method is called stigmatoscopy.

my depth. I propose to indicate a few of the more obvious implications. If I succeed in arousing a suspicion in the minds of some readers that perhaps the methods they have accepted from their teachers and found fairly satisfactory in practice may be capable of improvement, perhaps even should be abandoned for methods more in consonance with sound theory and tested practice, I shall be well repaid.

17. Ames, A., Jr., and Proctor, C. A.: J. Optic. Soc. America **5**:22, 1921.

My first plea is for a reform in the way the subject is taught. Recently, Edward Jackson,[18] in his last editorial, wrote as follows: "All the light coming from a certain luminous point and falling on a lens is brought to a focus in a single *point,* if it is a spherical lens, or a single *line,* if it is a cylindrical lens." (The italics are Jackson's.)

Now no one knew better than Jackson what Gullstrand had written. It is evident that he wished to give to the average ophthalmologist the old fictitious explanation. He would reserve for insiders—the elite, initiated few—the true cold facts. This reminds me of the old Egyptian priesthood, who had a body of truth for themselves, the insiders, and a body of make-believe for the common people. This is well shown by the Rosetta stone, on which was an inscription in the hieratic, demotic and Greek languages. The inside coterie, in this case the priests, by using an exclusive means of recording, the hieratic, were able to communicate their more esoteric thoughts to each other while keeping them from the common people (demos), who were restricted to the demotic language, used in every day transactions, while the Greek language served for foreigners. The same tendency to an exclusive inside body of ideas limited to the initiated few, while for the multitude of common people, outsiders, a different teaching is reserved, is seen in many, many instances from the Eleusinian mysteries to the Roman Catholic church. Even Jesus said, "I have yet many things to tell you but ye cannot bear them now."

I believe the time is ripe for teaching ophthalmologists the truth about the formation of images. Any one who has examined candidates for the certificate of the American Board of Ophthalmology in the subject of physiologic optics will bear me out that the present methods of teaching that subject have been a failure. Ophthalmologists do not use in their daily practice the stuff they have been taught. It is a waste of time to insist on it. Give them the truth in a practical exposition of what actually occurs in the human eye; they will perceive its practical value and, I believe, will take it in and use it.

Then they will begin to wonder about certain procedures. Finding that dilating the pupil increases greatly the aberrations, they will be prepared to doubt the supreme value of cycloplegia (when anything better than a rough approximation is aimed at), especially when they find that there are other effective ways of controlling the accommodation.

They will understand that any objective test—even so valuable a one as retinoscopy—can give only rough approximations, since, from the nature of the formation of images, only the person being tested can tell what point in the ray bundle suits him best, gives him the most serviceable image.

The chief difference in practice is that many methods in use give results that are rough approximations, not the exact measurements they are supposed to be by those who depend on them. I have already pointed out that progress in reducing the number of failures to relieve asthenopia is to be achieved by more exact measurement and more precise diagnosis of the errors of refraction and image formation. That is how progress was made in the last century; that is how it can be made now.

The challenge which Gullstrand's iconoclastic findings present to ophthalmologists is that they break away from the old teaching and seek better methods.

Let me end with a repetition of my leading motive, or theme:

"When a tradition once becomes established by the hall-mark of acknowledged authority, it takes more than cold facts to uproot it in men's minds—it takes time."

520 Commonwealth Avenue.

18. Jackson, E.: Am. J. Ophth. **25**:996, 1942.

LYMPHOMATOID DISEASES INVOLVING THE EYE AND ITS ADNEXA

JOHN S. McGAVIC, M.D.
NEW YORK

The lymphomatoid diseases are exceedingly complex. Little is known about their pathogenesis. Accurate classification of all the conditions included under this broad term is at present impossible. This is due in part to the use of different nomenclatures and different criteria for histopathologic and hematologic diagnosis of the recognized entities. Failure to regard lymphomatoid diseases as ever changing processes requiring repeated biopsies of tissue and repeated studies of the blood throughout the clinical course has delayed the adoption of a uniform classification of the many types of abnormal lymphoid reactions.

The chart prepared by Craver [1] lists the lymphomatoid diseases and indicates their interrelationships and the questionable position of some borderline conditions. Numerous papers [2] dealing at least in part with classification have appeared in the general literature; perusal of these will emphasize the difficulty of presenting any group of cases in such a manner that they will meet with the approval of all.

In an attempt to contribute toward a working basis for the management of patients with lymphomatoid diseases of the eye and its adnexa, this paper deals with a series of 21 verified cases. Of these, in 17 there was a primary tumor in the region of the eye, while in 4 ocular involvement appeared during the course

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From the Institute of Ophthalmology of the Presbyterian Hospital and the Head and Neck Clinic of the Memorial Hospital for the Treatment of Cancer and Allied Diseases.

1. Craver, L. F., in Pack, G. T., and Livingston, E. M.: Treatment of Cancer and Allied Diseases, New York, Paul B. Hoeber, Inc., 1940, p. 2488.

2. (*a*) Kundrat, H.: Ueber Lymphosarkomatosis, Wien. klin. Wchnschr. **6**:211, 1893; cited by Sugarbaker and Craver.[3] (*b*) Mallory, F. B.: Principles of Pathologic Histology, Philadelphia, W. B. Saunders Company, 1914. (*c*) Webster, L. T.: Lymphosarcoma, Lymphatic Leukemia, Leucosarcoma and Hodgkin's Disease, Bull. Johns Hopkins Hosp. **31**:458 (Dec.) 1920. (*d*) Desjardins, A. U., and Ford, F. A.: Hodgkin's Disease and Lymphosarcoma, J. A. M. A. **81**:895 (Sept. 15) 1923. (*e*) Keim, H. L.: The Lymphoblastomas: Their Interrelationships, Arch. Dermat. & Syph. **19**:533 (April) 1929. (*f*) Fraser, J. F.: The Interpretation of Mycosis Fungoides as a Variety of Lymphosarcoma, ibid. **11**:425 (April) 1925. (*g*) Brill, N. E.; Baehr, G., and Rosenthal, N.: Generalized Giant Lymph Follicle Hyperplasia of Lymph Nodes and Spleen, J. A. M. A. **84**:668 (Feb. 28) 1925. (*h*) Minot, G. R., and Isaacs, R.: Lymphoblastoma and Malignant Lymphoma, ibid. **86**:1185 (April 17); 1265 (April 24) 1926. (*i*) Symmers, D.: Certain Clinical and Pathological Aspects of Lymphosarcoma, Am. J. M. Sc. **174**:9 (July) 1927. (*j*) Warthin, A. S.: Genetic Neoplastic Relationships of Hodgkin's Disease: Aleukemic and Leukemic Lymphoblastoma and Mycosis Fungoides, Ann. Surg. **93**:153 (Jan.) 1931. (*k*) Roulet, F.: Weitere Beiträge zur Kenntnis des Retothelsarkoms der Lymphknoten und anderer Lymphoiden-Organe, Virchows Arch. f. path. Anat. **286**:702, 1932; cited by Sugarbaker and Craver.[3] (*l*) Callender, G. R.: Tumors and Tumor-Like Conditions of the Lymphocyte, the Myelocyte, the Erythrocyte and the Reticulum Cell, Am. J. Path. **10**:443 (July) 1934. (*m*) Krumbhaar, E. B.: Lymphomatoid Diseases (So-Called Lymphoblastomas), J. A. M. A. **106**:286 (Jan. 25) 1936. (*n*) Fraser, J. F., and Schwartz, H.: Neoplastic Disease of the Reticulo-Endothelial System, Arch. Dermat. & Syph. **33**:1 (Jan.) 1936. (*o*) Robb-Smith, A. H. T.: Reticulosis and Reticulosarcoma: A Histological Classification, J. Path. & Bact. **47**:457 (Nov.) 1938. (*p*) Sternberg, K.: Leukosarcomatosis, Beitr. z. path. Anat. **61**:75, 1916; cited by Krumbhaar.[2m] (*q*) Ewing, J.: General Pathology of Lymphosarcoma, Bull. New York Acad. Med. **15**:92 (Feb.) 1939; (*r*) Neoplastic Diseases, ed. 4, Philadelphia, W. B. Saunders Company, 1940. (*s*) Warren, S., and Picina, J. P.: Reticulum-Cell Sarcoma of Lymph Nodes, Am. J. Path. **17**:385 (May) 1941.

of already generalized lymphomatoid disease. Ophthalmologists are more concerned with cases such as those in the first group; secondary tumors, regardless of the sites involved, lie principally in the province of physicians skilled in the application of radiation therapy.

In each case a biopsy of the ocular tumor was made. Excluded from the series are cases of proved generalized disease with secondary ocular involvement unless a biopsy specimen was also taken from the affected ocular tissues. No case was included, whether the ocular tumor was primary or secondary, unless the histologic section was available for study by me and by the clinical pathologists consulted. These restrictions materially reduced the number of cases which could be reported but furnished a more accurate basis for correlating the clinical behavior of tumors of different histologic types. Notes concerning 16 additional cases, which do not fulfil these requirements, have been added because of the interesting variety of ocular manifestations; these are listed in table 1.

TABLE 1.—*Additional Cases in Which There Was Involvement of the Eye* *

	No. of Cases
1. Horner's syndrome from involvement of lymph nodes in the neck by Hodgkin's disease	1
2. Horner's syndrome from involvement of the cervical portion of the cord: metastasis to vertebrae by Hodgkin's disease	1
3. Papilledema and retinal hemorrhage from involvement of the optic nerve and intracranial involvement by Hodgkin's disease	1
4. Bilateral papilledema, retinal hemorrhage and field changes caused by reticulum cell lymphosarcoma in the sphenoid region	1
5. Mycosis (granuloma) fungoides involving the skin of the face and eyelids	2
6. Leukemic retinopathy, especially hemorrhages associated with severe anemia	3
7. Involvement of the lids and subconjunctiva by lymphatic leukemia	1
8. Involvement of the lids and subconjunctiva by lymphocytic cell lymphosarcoma	3
9. Plasmoma of the conjunctiva (trachoma in 1 case and no evidence of inflammation in 1)	2
10. Chloroma, with the first tumors appearing in the eyelids	1
Total	16

* These represent lymphomatous diseases with indirect involvement of the eye or direct involvement without sufficient data to be included with the 21 cases analyzed in this study. The diagnosis in all these cases has been proved by biopsy or postmortem examination.

INCIDENCE

Lymphomatoid diseases occur at all ages and in both sexes. They may occur at any site in the body but more frequently appear in the recognized lymphatic tissues. Lymphoid leukemia may be a primary disease or may occur during the course of lymphosarcoma.

Sugarbaker and Craver [3] reported that extranodal primary foci occurred in only one third of their cases, and of these 65 per cent were in the head and neck. Of all the extranodal primary lesions, 1 per cent were in the orbit and eyelid. They found that in 1.5 per cent of all their cases of generalized lymphosarcomatosis there was secondary involvement of the orbit, lacrimal gland or conjunctiva.

The 18 biopsy specimens of lymphomatoid tumors in the pathology laboratory of the Institute of Ophthalmology of the Presbyterian Hospital represent 2.65 per cent of all the specimens of extrabulbar tumors. A single lymphoid tumor of the iris is the only such iris tumor in the same collection. Three of the specimens are from the Head and Neck Clinic of the Memorial Hospital for the Treatment of Cancer and Allied Diseases.

3. Sugarbaker, E. D., and Craver, L. F.: Lymphosarcoma: A Study of One Hundred and Ninety-Six Cases with Biopsy, J. A. M. A. **115**:17 (July 6); 112 (July 13) 1940.

Table 2 shows the incidence of the various histologic types of tumors in this series of 21 cases, of which the patient was male in 11 and female in 10. The average age was 55.5 years. Except for 1 patient, aged 29 years (with Hodgkin's disease), all were over 45. All of the patients were white.

Table 3 shows the sites involved by the tumors.

DIAGNOSIS

The diagnosis of lymphomatoid diseases must be established by histopathologic examination. Incisional biopsies are necessary; aspiration biopsies too often fail to give sufficient information to warrant a diagnosis. Unfortunately, even diagnosis from biopsies is sometimes inconclusive or confusing, since tissues taken

TABLE 2.—*Classification of the Tumors in the 21 Cases as to Histologic Type*

Lymphocytic cell lymphosarcoma *	2
? Simple lymphoma or lymphocytic cell lymphosarcoma †	6
Giant follicular lymphosarcoma (generalized)*	1
? Giant follicular lymphosarcoma (localized)†	2
Reticulum cell lymphosarcoma	7
Lymphosarcoma, unclassified	1
Hodgkin's disease	1
Lymphocytic cell lymphosarcoma or simple lymphoma of the iris †	1
Total	21

* Leukemia has developed in the course of generalized disease in 2 cases.

† The exact histologic classification has not been agreed on, as noted in the text. Two outstanding clinical pathologists were consulted, and their opinions are given. The future clinical course of the patients will decide the issue.

TABLE 3.—*Sites of the Tumors in This Series*

		Total	Primary
Subconjunctiva		5	5
Lacrimal gland		7	5
Orbit (excluding lacrimal gland)		3	2
Lids and brow		5	..
Lids alone	3	..	3
Brow alone	1	..	0
Lids and orbit	1	..	1
Iris		1	1
Total		21	17

from the same patient at different stages, or even at almost the same time from different parts of the body, may not show identical pictures microscopically (case 18). Early in the clinical course a biopsy may show an inflammatory type of reaction or what appears to be a benign proliferation of lymphoid tissue, while later biopsies show undoubted evidence of malignant growth, the patient meanwhile having the usual progressive course (case 16).

Repeated differential blood counts and studies of the bone marrow may be necessary to rule out or demonstrate leukemic changes. Since the blood picture is constantly changing, one must consider not only the type of hemogram but the time at which changes occur. True leukemia may be present as the original disease, may appear late in the course (cases 1 and 18) or may never appear. Leukemoid blood pictures necessitate careful differentiation.

Krumbhaar [2m] has emphasized the necessity of providing the pathologist with all the available data before expecting an accurately classified diagnosis or a

prognosis. Even with this aid, to arrive at a diagnosis and prognosis is often difficult. There is perhaps no greater contrast in the field of tumors than that between the precision possible in microscopic grading, standardization of treatment and accuracy of prognosis for epitheliomas of the skin and the unsettled status of the same factors for lymphomatoid tumors.

With regard to diagnosis and classification of the tumor in the cases in this series, differences of opinion were encountered in 8. Two cases of tumor of the lacrimal gland (cases 19 and 20) have been reported by Wheeler [4] and Perera [5] as instances of giant follicular lymphosarcoma. Dr. A. P. Stout also made this diagnosis, adding that giant follicular lymphosarcoma has a relatively slow course but is nevertheless malignant and may in the end destroy the host. Dr. F. W. Stewart stated the belief that lymphosarcoma of the orbit does not fall into the same clinical category as that of lymph nodes. He would regard the same lesion in a lymph node as a giant follicular lymphosarcoma and expect it to generalize and have a fatal outcome. He felt justified in calling the tumors in these cases nonspecific lymphogranulomas (not Hodgkin's disease) and anticipated a benign course. He was doubtful that they were neoplastic in origin. In both cases the tumor was excised and radiation therapy was given postoperatively. Both patients were alive and well five years after operation. One can only surmise what the outcome might have been had the tumors not been treated when they were first seen.

In 6 other cases (cases 3, 4, 5, 6, 7 and 8) the classification remains in question. The greatest difficulty was met in attempting to classify tumors made up of small cells of the lymphocytic series. Stewart [6] stated the belief that they were simple lymphomas and probably not neoplastic in origin. Stout [7] said that such extensive infiltration of small cells of the lymphocytic series can occur only in leukemia or lymphocytic cell lymphosarcoma. His criteria for diagnosis were given in a recent paper,[8] in which 218 cases of lymphosarcoma were reviewed. Stout expressed the opinion that these 6 cases were instances of neoplastic growth and that, although the clinical course had been benign so far, there was nevertheless a possibility of malignant spread and/or leukemia. In 1 of the cases there were an involvement of the lid and one of the orbit. In the other 4 cases the tumor was subconjunctival. Four circumscribed tumefactions appearing as glossy, salmon-colored elevated masses beneath the bulbar or palpebral conjunctiva were similar to those described by Bedell,[9] Ennema,[10] Löwenstein,[11] Coats,[12] Wright,[13] Saradarian,[14] Shannon and McAndrews [15] and others. Bedell inoculated animals and cultured the excised tissue with negative results.

4. Wheeler, M. C.: Malignant Neoplasm of the Eyelid, Arch. Ophth. **20**:682 (Oct.) 1938.

5. Perera, C. A.: Lymphosarcoma of the Lacrimal Gland: Report of a Case with Giant Lymph Follicle Hyperplasia, Arch. Ophth. **28**:522 (Sept.) 1942.

6. Stewart, F. W.: Personal communication to the author.

7. Stout, A. P.: Personal communication to the author.

8. Stout, A. P.: Is Lymphosarcoma Curable? J. A. M. A. **118**:968 (March 21) 1942.

9. Bedell, A. J.: A Case of So-Called Solid Edema, Lymphoma, Tr. Am. Acad. Ophth., p. 201.

10. Ennema, M. C.: Lymphoma Conjunctivae, Acta ophth. **13**:225, 1935.

11. Löwenstein, A.: Leukämische und aleukämische epibulbar Lymphome, Klin. Monatsbl. f. Augenh. **61**:571, 1918.

12. Coats, G.: Discrete Lymphoid Infiltration of the Orbit, Arch. Ophth. **44**:221, 1915; Lymphoma and Lymphosarcoma of the Conjunctiva, ibid. **44**:235, 1915.

13. Wright, R. E.: Lymphomata of the Orbit, Lancet **1**:124 (Jan. 19) 1929.

14. Saradarian, A. V.: Bilateral Subconjunctival Lymphoid Infiltration, Arch. Ophth. **24**: 980 (Nov.) 1940.

15. Shannon, C. E. G., and McAndrews, L. F.: Lymphomas of the Conjunctiva, Am. J. Ophth. **15**:821 (Sept.) 1932.

In this series there were 5 subconjunctival tumors showing three different microscopic pictures:

1. Small round cells of the lymphocytic series which show uniform size and staining, few mitoses and little evidence of invasion (cases 3, 4 and 5).
2. A similar picture with the addition of some slightly larger cells, more mitoses and some cells suggesting a possible leukemic change to both Dr. Stout and Dr. Stewart (case 6).
3. Cells with such marked variation and aplasia that classification was impossible. The tumor looked most like malignant lymphocytoma (case 17).

Ennema [10] has reported follicular structure in subconjunctival growths (so-called lymphadenosis), but such structure was not encountered in the series here reported. His patients were young, and from the descriptions one thinks of folliculosis of the conjunctiva. The important thing is that all of these tumors had the same clinical appearance but differed in the microscopic picture and clinical course.

In case 8, the patient gave a history of exophthalmos of ten years' duration due to a tumor with the same histologic picture as the four subconjunctival tumors which have so far followed a benign course. One year later a mass developed in the cheek and was treated until regression by roentgen radiation. Permission for biopsy was not obtained. At the time of writing there are no palpable lymph nodes, and the blood and sternal marrow are normal. However, the development of a second mass is suggestive of a malignant growth.

PROGNOSIS

In general the outlook for patients with lymphomatoid disease is poor. Most reports deal with the prognosis of the various types of lymphosarcoma and Hodgkin's disease. Minot and Isaacs,[2h] Desjardins and Ford,[2d] Warthin [2j] and Krumbhaar [2m] have expressed themselves as extremely pessimistic.

Sugarbaker and Craver [3] reported a determinate group of 132 cases (out of a total of 196 cases) of lymphosarcoma with a five year survival rate of 15.9 per cent and with 10.6 per cent of the patients apparently cured after a period of five years.

Stout [8] reported a study of 218 cases of lymphosarcoma with a five year survival rate of 16.5 per cent and with 10.5 per cent of all patients symptom free after five years, while of the treated patients 14.8 per cent were symptom free after the same period. When the follow-up period was extended to ten years, he found 6.7 per cent of all patients, 12.5 per cent of treated patients and no untreated patients symptom free. However, 8.9 per cent of all patients, 14.6 per cent of treated patients and 2.4 per cent of untreated patients were alive, with or without tumor, after ten years. Stout stressed particularly the variation in survival rates and apparent cures according to the histopathologic type of lymphosarcoma. He clearly stated the simplified criteria used in the classification of his cases.

These two reports emphasized the fact that long survival is dependent largely on treatment of the disease while it is still localized. The authors found that youthful patients have a more rapid and fatal course than do older patients. Leukemia was uniformly fatal and occurred in 2.3 per cent of Stout's cases and in 6.6 per cent of Sugarbaker and Craver's cases.

Table 4 shows the present status in the 21 cases in the present series.

It is much easier to give a prognosis for histologically malignant lymphomatous processes than for those which show less histologic evidence of malignant growth. Sugarbaker and Craver noted that lymphosarcoma primary in the head or neck tends to follow a less malignant course than that arising elsewhere in

the body. Such growth in the region of the eye produces signs and symptoms which cause the patient to seek medical advice earlier and hence more often while the disease is still localized. One may therefore argue that a higher percentage of patients with this malignant tumor about the eye are cured by virtue of early treatment rather than because ocular lymphoma is generally less malignant than lymphoma occurring elsewhere. Another factor to be considered is the relative paucity of lymphoid tissue in the region of the eye; this probably accounts for the small percentage of primary tumors rather than for the lowered tendency for them to become generalized, because lymphomatoid diseases do not always spread to neighboring lymph nodes with the orderly progression that one sees in carcinoma. Indeed, the preauricular gland was involved less often in cases of primary tumor of the region of the eye than in cases of generalized disease with secondary involvement of the eye. Several sites with small amounts of lymphoid tissue are favored sites for secondary involvement, for example, the testis. In cases 10 and 14 in this series there was secondary involvement of the testis.

To return to the 4 subconjunctival lesions which have not shown a tendency to recur, spread or be complicated by leukemia, it does not seem safe to give a prognosis at this time. All one can say is that so far they have behaved like

TABLE 4.—*Present Status in the 21 Cases*

Tumors primary in the region of the eye			17
Remained localized		11	
Later spread		6	
Patient alive	4		
Patient dead	2		
Disease generalized before involvement of the eye			4
Patient alive		1	
Patient dead		3	

benign lesions; yet histologic sections from them cannot be differentiated with any degree of accuracy from some sections from patients known to have generalized disease. Extending the follow-up period to ten years and studying reports by other observers will help to clear up the uncertainty with regard to this group of lymphocytic cell tumefactions.

Verhoeff [16] stated after examining the sections that he had examined many other such specimens of lymphoma of the conjunctiva and could recall no cases in which lymphoma was present elsewhere in the body.

The fact that Knapp [17] successfully expressed the lymphoid tissue from the palpebral conjunctiva with roller forceps without any recurrence or evidence of spread in two years' time speaks for a benign type of lesion.

It should be noted again, however, that the clinical appearance of the subconjunctival lesion was the same in the 4 cases in which the course has been benign as in the 1 case (case 17) in which the sections examined histologically showed malignant tumor, which later spread to other parts of the body.

TREATMENT

Surgical intervention should be limited to biopsy, unless the mass is encapsulated and can be removed without sacrifice of function.

16. Verhoeff, F. H.: Personal communication to the author.
17. Knapp, A.: Personal communication to the author.

Practically all lymphomatoid growths are radiosensitive, but this quality must be differentiated from radiocurability. A given lesion may be treated to complete regression, but this does not preclude the appearance of tumor masses at other sites. Local recurrence after treatment of a primary tumor in the region of the eye has not occurred in the series of 17 cases, but a general spread has occurred after such treatment in 6 of these cases (table 5).

Immediately successful treatment of a tumor in the region of the eye does not relieve the ophthalmologist or the physician giving the radiation from further care of the patient. Many reports demonstrate the necessity of five to ten years' follow-up. After receiving a report from the pathologist, the clinician should refer the patient to a physician skilled in the application of radiation therapy. If, however, at a later date lymph nodes become palpable, a second biopsy is advisable before further treatment, not only to show whether or not the enlarged nodes represent manifestations of the same tumor but to add to the knowledge of the life cycle of lymphoid disturbances.

Craver [18] has stated that the lymphomatoid diseases "are so variable and unpredictable that their treatment by irradiation has remained an art rather than a science to a degree greater than is true for so many of the malignant tumors." Especially in the region of the eye, radiation is a two-edged sword. In this series

TABLE 5.—*Present Status in the 21 Cases*

	Number	Primary Tumor
Patient alive and without evidence of tumor.....	11	11
Average, 4.0 years (on record)		
Average, 5.2 years (history)		
Patient alive with tumor.....	5	4
Average, 3.7 years		
Patient dead.....	5	2
Average, 4.0 years		

an eye was unavoidably lost in 3 cases as a result of radiation glaucoma, and in a fourth case radiation cataracts requiring operation developed. In all 4 of these cases there was a malignant tumor so situated that adequate protection of the anterior segment could not be afforded.

In all of the cases in this series except case 21 (an instance of Hodgkin's disease) and case 4 (in which Dr. Knapp expressed the lymphoid tumor with roller forceps), radiation therapy was used. In case 15 the entire lacrimal gland was excised, and troublesome secondary keratitis sicca developed. This complication has not been noted after radiation therapy of the lacrimal gland, as the lymphoid cells are more radiosensitive than the lacrimal gland itself. In this case it was later necessary to use radiation therapy in addition to surgical excision.

If the site of surgical treatment is not visible or readily palpable, it is safest to follow surgical intervention with radiation therapy. The dose of radiation in the region of the eye should obviously be the least amount which will destroy the tumor, and great care should be used in shielding the anterior segment of the globe.

Dr. Hayes Martin believes that lymphoma and lymphosarcoma in the region of the head and neck should be considered as having a local, single origin rather than a multiple origin. Therefore, he believes that they should be treated in much the same way as carcinoma is treated. The results of treatment of such tumors in the Head and Neck Clinic of the Memorial Hospital for the Treat-

18. Craver, L. F.: Irradiation in the Lymphomatoid Diseases, Bull. New York Acad. Med. **15**:442 (July) 1939.

ment of Cancer and Allied Diseases certainly justifies this point of view. In this series, 11 of the 17 primary tumors remained localized and did not recur after treatment. Martin and Sugarbaker [19] have reported five year cures in 20 per cent of cases of lymphosarcoma of the tonsil. One can employ the same radiation set-up advocated by Martin and Reese [20] for the treatment of retinoblastoma.

REPORT OF CASES

The data regarding the 21 cases in this series are summarized in table 6. Several case reports have been added to illustrate various points mentioned in the text.

CASE 3.—G. K., a man aged 55, was first seen in May 1940. He gave a history of having had elevated reddish masses over the upper portion of each eyeball for the previous sixteen years. These had gradually increased in size. There was no history of preceding or concurrent inflammation. Examination revealed bilateral, almost symmetric, elevated coral-colored masses beneath the upper bulbar conjunctivas. Numerous elevated conglomerate follicle-like excrescences were present beneath the lower palpebral conjunctiva of each eye. A biopsy specimen was taken from the epibulbar mass of the left eye and showed a solid infiltration of small round cells with little supporting structure. Many capillaries were present. There was little variation in the size and staining characteristics of the cells. The patient was treated by radiation.

When the eyes were examined again, in March 1942, the epibulbar masses had undergone complete regression. The untreated palpebral conjunctiva showed approximately the same amount of lymphoid infiltration as in 1940. The patient was referred for further radiation therapy after a second biopsy showed the same type of lymphocytic cell tumor.

CASE 18.—A. H., a woman aged 52, had had biopsies of specimens from various sites in the body showing the typical features of giant follicular lymphosarcoma (Brill-Symmer's disease). The first of these was taken in July 1940, five years after the onset of symptoms. The left lacrimal gland became involved in December 1941, and a biopsy specimen was taken before radiation was employed. The sections showed a diffuse infiltration of lacrimal gland tissue by small, round, blue-staining cells of the lymphocytic series. No follicle formation was present. The patient has shown moderate changes in the blood and bone marrow indicative of early lymphatic leukemia.

The histologic picture of the lacrimal gland was exactly like that seen in the 6 cases (3, 4, 5, 6, 7 and 8) which have offered so much difficulty in classification. In this case the generalized disease preceded the ocular involvement and made classification of the growth possible. Otherwise, it would have been called "simple lymphoma or lymphocytic cell lymphosarcoma."

This case illustrates three points previously mentioned: (1) that biopsy specimens from different sites may show different histopathologic pictures, (2) that the prognosis often cannot be made accurately from a single biopsy specimen and (3) that leukemia may occur late in the course of lymphosarcoma. Leukemia in association with giant follicular lymphosarcoma is infrequent (Stout, 1 case; Craver and Sugarbaker, 1 case).

Birch-Hirschfeld,[21] Benedict and Knight,[22] Reese [23] and Lewis [24] have reported on "pseudotumor" of the orbit, a granulomatous inflammatory mass of unknown

19. Martin, H., and Sugarbaker, E. L.: Cancer of the Tonsil, Am. J. Surg. **7**:155 (April) 1941.

20. Martin, H. E., and Reese, A. B.: Treatment of Retinoblastoma (Retinal Glioma) Surgically and by Irradiation, Arch. Ophth. **27**:40 (Jan.) 1942.

21. Birch-Hirschfeld, A.: Die Krankheiten der Orbita, in Graefe, A., and Saemisch, F.: Handbuch der gesamten Augenheilkunde, ed. 2, Berlin, Julius Springer, 1930, vol. 9, pt. 1, p. 501.

22. Benedict, W. L., and Knight, M. S.: Inflammatory Pseudotumor of the Orbit, Arch. Ophth. **52**:582 (Nov.) 1923.

23. Reese, A. B.: The Etiology of Exophthalmos, Tr. Am. Acad. Ophth. **39**:65, 1934.

24. Lewis, P. M.: Inflammatory Pseudotumor of the Orbit, Am. J. Ophth. **21**:991 (Sept.) 1938.

TABLE 6.—*Summary of the 21 Cases*

Case No.	Patient	Age	Sex	Diagnosis	Site	Onset of Ocular Lesion	Onset of Other Lesions	Patient Dead or Alive, April 1942	Patient Alive with Tumor	Hemogram
1	J. M.	60	M	Lymphocytic cell lymphosarcoma	Lids both eyes	1932	1935	Died 1936	..	Leukemia
2	S. B.	63	M	Lymphocytic cell lymphosarcoma	Lacrimal gland	April 1941	None	Alive	..	Normal
3	G. K.	55	M	Lymphoma or lymphocytic cell lymphosarcoma	Subconjunctiva, both eyes	1924 (history)	None	Alive	..	Normal
4	L. J.	56	M	Lymphoma or lymphocytic cell lymphosarcoma	Subconjunctiva, both eyes	1938	None	Alive	..	Normal
5	T. K.	45	F	Lymphoma or lymphocytic cell lymphosarcoma	Subconjunctiva, left eye	1940	None	Alive	..	Normal
6	J. J.	52	M	Lymphoma or lymphocytic cell lymphosarcoma	Subconjunctiva, both eyes	1939	None	Alive	..	Normal
7	R. S.	59	F	Lymphoma or lymphocytic cell lymphosarcoma	Lid	1937	None	Alive	..	Normal
8	M. K.	61	F	Lymphoma or lymphocytic cell lymphosarcoma	Left orbit	1940	1941	Alive	+	Normal
9	M. J.	50	F	Lymphoma or lymphocytic cell lymphosarcoma	Iris	1936	None	Alive	..	Not available
10	W. R.	47	M	Reticulum cell lymphosarcoma	Lacrimal gland	1941	1941	Alive	+	Not available
11	C. N.	53	F	Reticulum cell lymphosarcoma	Lid	1939	None	Alive	..	Not available
12	A. S.	70	F	Reticulum cell lymphosarcoma	Lid and orbit	1937	1939	Died 1940	..	Not available
13	J. S.	64	M	Reticulum cell lymphosarcoma	Lacrimal gland	1934	1927	Died 1935	..	Not available
14	R. T.	50	M	Reticulum cell lymphosarcoma	Orbit	1937	1937	Died 1938	..	Not available
15	C. K.	59	F	Reticulum cell lymphosarcoma	Lacrimal gland	1939	None	Alive	..	Not available
16	M. H.	60	F	Reticulum cell lymphosarcoma	Orbit, both eyes	1931	1933	Alive	+	Not available
17	S. Z.	54	M	Lymphosarcoma (unclassified)	Subconjunctiva	1940	1940	Alive	+	Normal
18	A. H.	52	F	Giant follicular lymphosarcoma	Lacrimal gland	1940	1940	Alive	+	Leukemia
19	E. G.	59	F	Lymphoma or giant follicular lymphosarcoma	Lacrimal gland	1937	None	Alive	..	Normal
20	J. W.	68	M	Lymphoma or giant follicular lymphosarcoma	Lacrimal gland	1937	None	Alive	..	Normal
21	J. S.	29	M	Hodgkin's disease	Brow	1939	1934	Died 1936	..	Normal

causation which runs a self-limited course ending in complete regression, often with enophthalmos. Reese analyzed 30 cases in the literature and found that in 50 per cent of them the patient had been subjected to exenteration of the orbit for supposed malignant neoplasm. Lewis stressed the difficulty of getting the correct diagnosis from many general pathologists, who he found are more likely to report that the biopsied tissue represents a true neoplasm.

In 1 of the cases of the present series (case 16) the patient presented the typical clinical picture of a pseudotumor (granuloma) of the right orbit.

CASE 16.—M. H. was a woman aged 60. The description of the original biopsy specimen was compatible with a diagnosis of pseudotumor (granuloma) of the orbit. Two years later proptosis of the left eye developed and a clinical diagnosis of granuloma was again made. Three years later the exophthalmos on the left side recurred. No biopsy specimens were taken. Dr. A. B. Reese remarked that this was the first case in which pseudotumor had been bilateral and in which recurrence had been observed. Subsequently generalized lymphadenopathy developed, and on biopsy of a supraclavicular lymph node a diagnosis of reticulum cell lymphosarcoma was made.

Recently I have been fortunate enough to obtain a section of the original biopsy specimen from the left orbit. To my surprise the microscopic picture was quite different from the typical picture described so well by Benedict and Knight; nor could the condition represented by this section be definitely diagnosed as one of the lymphomatoid diseases, although one could suspect that a portion of the tissue showed evidence of lymphoid infiltration unlike that of granuloma and suggestive of lymphosarcoma. In view of the subsequent clinical course and the results of a biopsy of a supraclavicular lymph node, it became clear that the disease was a changing lymphomatoid process which first appeared to be an inflammatory process.

One must agree with Lewis that pseudotumor is an entity peculiar to the field of the ophthalmologist and that an ophthalmic pathologist may be of great help in interpreting the sections. In the case reported the disease would have been recorded as lymphosarcoma developing from a granuloma had one relied entirely on the original description and report.

A second case, not included in this series because a conclusive biopsy specimen has not yet been obtained, has followed almost the same clinical course.

These 2 cases provide evidence that an orbital lesion first clinically characteristic of pseudotumor (granuloma) may later be accompanied with diffuse malignant lymphomatoid disease. When the microscopic picture does not meet the criteria of Benedict and Knight, if the second orbit becomes involved or if general lymphadenopathy occurs, one must assume that the original lesion was not a granuloma and one may suspect a lymphosarcoma. Rapid response to radiation is against the diagnosis of a pseudotumor.

CASE 9.—M. J., a woman aged 50, had a radical mastectomy performed by Dr. L. R. Kauffman at the Fifth Avenue Hospital in 1934. The microscopic diagnosis was infiltrating carcinoma. In 1936 the patient was seen by Dr. John Conboy and Dr. John M. Wheeler because of a tumor of the iris. A clinical diagnosis of metastatic carcinoma was made, and the eye was enucleated. Sections of the eye showed a lymphomatous tumor of the iris which was considered a lymphocytic cell lymphosarcoma or a benign lymphoma. The patient was alive and well six years after enucleation.

This case is interesting for two reasons: (1) So far as is known, it is the first reported instance of a primary lymphoma of the iris, and (2) it illustrates the occasional occurrence of multiple primary tumors in the same patient. The latter is a further reason for advising biopsies of secondary tumefactions in patients with known lymphomatoid disease. Hartshorne [25] has reported (1922) a lympho-

25. Hartshorne, I.: Lymphosarcoma of the Orbit, Probably Arising in the Choroid, Am. J. Ophth. **5**:604 (Aug.) 1922.

sarcoma of the orbit, apparently arising in the choroid. In his case permission for enucleation was refused; the tumor finally ruptured through the sclera into the orbit and became generalized.

CASE 21.—J. S., a man aged 29, had had previous biopsies beginning in 1934, showing the classic picture of Hodgkin's disease. When his lid and brow became involved, the mass was surgically excised. Sections showed a histologic picture somewhat atypical of Hodgkin's disease, but because it is not uncommon to observe dissimilar biopsy specimens from different areas, the diagnosis was made definitely.

Kravitz [26] and Avery and Warren [27] reported a case in which the original diagnosis was made from a tumor mass excised from the eyelid. O'Brien and Leinfelder [28] reported in 1935 subconjunctival lesions as manifestations of Hodgkin's disease.

In another case (not included in the series of 21) a primary tumor of the brow was excised by Dr. J. M. Wheeler in 1927. The sections showed a markedly sclerosing inflammatory process barely suggestive of Hodgkin's disease. The patient's subsequent course and response to radiation were typical of Hodgkin's disease, with the fatal outcome four years later. No necropsy was performed.

SUMMARY AND CONCLUSIONS

Twenty-one histologically proved cases of lymphomatoid diseases involving the eye and its adnexa, with an average follow-up of four years, are reported. Notes on 16 additional cases are included.

The difficulties in microscopic diagnosis, classification and prognosis are discussed.

Repeated tissue biopsies and differential blood counts throughout the clinical course are advocated as the best means of clarifying the status of the lymphomatoid diseases. Patients must be followed for long periods before conclusions can be drawn as to the behavior of certain tumors.

Tumors made up of small cells of the lymphocytic series represent an interesting type whose classification is important, but as yet unsettled.

Subconjunctival "lymphomas" have the same clinical appearance irrespective of the histologic type and clinical course.

A primary lymphoma of the iris is reported.

A study of the present series and of the general medical literature suggests that the lymphomatoid diseases represent a great variety of related clinical and histologic responses by lymphoid tissue to currently unknown stimuli. Some of the tumors appear to be neoplastic from their onset, while others may represent transitions from inflammatory to neoplastic lesions.

Despite the generally poor prognosis for patients with localized lymphomatous tumors in the region of the eye, these tumors should be actively treated by radiation, just as one treats carcinoma, with the justified hope that some of the patients will be cured and not have generalized lymphosarcomatosis (11 of 17 primary tumors in this series remained localized).

635 West One Hundred and Sixty-Fifth Street.

ABSTRACT OF DISCUSSION

DR. WILLIAM L. BENEDICT, Rochester, Minn.: Both the clinician and the pathologist are sometimes at a loss to know how to classify certain tumors of the eyelids and the orbit that appear to have their origin in the lymphatic system or

26. Kravitz, D.: Hodgkin's Disease of the Lid, Arch. Ophth. **21**:844 (May) 1939.
27. Avery, J. W., and Warren, J. W.: Unusual Case of Hodgkin's Disease, Arch. Ophth. **26**:1019 (Dec.) 1941.
28. Leinfelder, P., and O'Brien, C. S.: Lymphoma of the Eye and Adnexa, Arch. Ophth. **15**:183 (Aug.) 1935.

are closely related to that system by anatomic distribution or by cellular structure. Clinical pictures of the lymphatic neoplasms are recognized by enlargement of the neck and of the face, by growth in the lymph nodes and involvement of the glands and, in late stages of the disease, by infiltration of nearly all parts of the body.

There are no clinical characteristics by which primary lymphomas of the orbit can certainly be recognized. Other lymphogenous masses that occur about the orbit and eyelids, whether primary or the result of metastasis or extension, usually have some features that are common to all lymphatic diseases, such as greatest involvement in and about the glands and lymph nodes, rapid growth, invasion of surrounding tissue, a tendency to spread rather than to become encapsulated and a tendency to break down under roentgen ray treatment and to form cystic masses. Invasion of the orbit by lymphogranuloma, whether by direct extension from the face and sinuses or by metastasis from tumors situated in the trunk, occurs as a part of the generalized involvement that soon leads to a fatal issue. The histopathologic picture, also, is sometimes not clear, and a definite diagnosis by means of biopsy is not always possible. A difference of opinion regarding the pathologic diagnosis, as mentioned by Dr. McGavic, is due to the bizarre cellular elements that are often found in lymphogenous diseases and to the fact that little is known of their origin.

Gall and Mallory have favored the term "malignant lymphoma" for those maladies of the lymphatic system which are characterized clinically by progressive tumor-like enlargement of lymphoid tissue with eventual death (Gall, A. G., and Mallory, T. B.: *Am. J. Path.* **18:** 381-415 [May] 1942). Within this classification are seven categories based on cellular form and architecture: (1) steam cell lymphoma, (2) clasmatocytic lymphoma (these two being reticulum cell sarcoma), (3) lymphoblastic lymphoma, (4) lymphocytic lymphoma, (5) Hodgkin's lymphoma, (6) Hodgkin's sarcoma and (7) follicular lymphoma. So-called lymphosarcoma is not confined to any one of these categories, nor is there any complete clinical picture with which the neoplasm is consistently associated. The occurrence of isolated malignant lymphoma in areas in which even isolated lymph follicles are not found under normal circumstances is of marked interest and importance. "Localization is not a peculiarity of any cytologic type of lymphoma but is met in all" (Gall and Mallory, page 403).

Besides malignant lymphomas there are other lymphogenous tumors and lymphatoid diseases that occasionally are found about the orbit. Mikulicz' disease is a lymphatic disease that involves the eyelids and the lacrimal and salivary glands and is characterized by marked swelling of the lids and face. The histopathologic picture is not constant, but the lymphatic tissue is predominantly involved. A fatty xanthomatous tumor of the calvarium diagnosed as chloroma was found in a child with extensive necrosis of the bone and exophthalmos. While most of the lymphoid tumors are amenable to treatment with roentgen rays, I agree with Dr. McGavic that many of them are not curable. Surgical removal is justified in cases of isolated tumor of the orbit, regardless of the pathologic report from a biopsy. The pathologist cannot classify any malignant lymphoma as radiosensitive on the basis of the histologic picture alone; the clinical picture presented by the patient gives the most reliable criteria. As a matter of fact, it is common practice to treat with radiation all malignant and nearly all nonmalignant lymphatic processes because of the inability to determine which are not remediable.

I have removed isolated orbital lymphosarcoma in 9 cases. The duration of signs of tumor was from one and a half months to three years, the average being eleven weeks. The patients were from 36 to 78 years old. They are all still living after one to eight years, the average period being more than three years. On 2 patients not operated on, aged 12 and 33, I have no follow-up data. One patient with epibulbar lymphosarcoma and metastases died four months after operation and less than one year after the tumor first appeared.

I have records on 10 patients with malignant lymphoma of the orbit produced by metastasis or extension. Of these, 4 were less than 16 years of age; the oldest

was 68, and the average age was 38. In this group the mortality was high; several patients did not survive a year after the orbit was invaded.

Three patients with Mikulicz' disease have been observed, one over a period of twenty years, one for four years and one for nearly five years. The disease is not cured but is arrested by radiotherapy. One patient with chloroma was cured by operation and subsequent irradiation. A patient aged 10 months with Christian's disease was treated by radiotherapy and completely recovered. One patient with lymphangioma of the eyelids for thirteen years has not improved although operation and radiotherapy have been employed.

I have no reason to believe that the patients with chronic inflammatory pseudotumor on whom I have reported elsewhere had lymphogenous diseases, yet I cannot deny a resemblance to certain pathologic pictures found in other clinical conditions thought to be of lymphogenous origin.

DR. BENJAMIN RONES, Washington, D. C.: Dr. McGavic has well presented a group of diseases that deserve notice if for no other reason than their exceeding complexity and the difficulties of accurate diagnosis.

Among 11,500 ocular specimens in the Army Medical Museum I could find only 19 lymphomatous tumors. Of these, 5 were easily classified as representing leukemia, either myeloid or lymphatic in type, and occasioned no difficulty in pathologic diagnosis. Two were diagnosed as benign lymphoma of the conjunctiva. The remaining 12 were malignant lymphoblastoma or lymphosarcoma. One of these involved the conjunctiva, with no evidence of disease elsewhere. It was treated with radium, and there had been no recurrence eleven years later. Five had involved the orbit, requiring removal of the eye or exenteration of the orbit. Several of these specimens were circulated among the consultant pathologists of the Lymphatic Tumor Division at the Army Medical Museum, with some rather wide discrepancies in the resultant pathologic diagnoses. In one instance two pathologists diagnosed malignant lymphocytoma, two nodular lymphocytoma and another inflammatory pseudotumor of the orbit. In another instance four consultants diagnosed aleukemic lymphocytoma, while another called the condition small cell melanoma.

All this is by way of emphasizing the difficulties of both clinical diagnosis and pathologic interpretation of these conditions. G. R. Callender, in an excellent article (Tumors and Tumor-Like Conditions of Lymphocyte, Myelocyte, Erythrocyte and Reticulum Cell, *Am. J. Path.* **10:** 443 [July] 1934), has attempted to organize this chaos on the basis of the material in the Lymphatic Tumor Division. Several paragraphs from his paper are well worth emphasizing:

"In this group arising from the lymphocyte there is considerable shifting from one subdivision to another, both spontaneously and as a result of irradiation. For instance a leukemia may terminate in a lymphosarcoma, or may become aleukemic. Leukemic or aleukemic lymphocytoma may become sarcomatous. In all aleukemic cases in the Registry from which blood films have been furnished abnormal lymphocyte types have been found, while frequently during the course of the disease a definite lymphocytosis is present even though a frank leukemia never appears.

"Lymphosarcoma usually appears and continues as such. Occasionally, as indicated by the literature, a combination of a metastasizing tumor and a leukemia occurs (leukosarcoma) and may be the condition discovered at primary examination. In the Registry material a condition of leukemia has followed irradiation of lymphosarcoma in six instances and in these the progress of the disease has appeared to have been retarded as a result of the change."

The most important point is the distinction between the benign and the malignant. It must be borne in mind that secondary inflammatory follicles of lymphoid tissue are common any place in the body, but particularly so in the conjunctiva. Frequently specimens are sent to the laboratory with the clinical diagnosis of lymphosarcoma and on section are found to be secondary inflammatory nodules.

DR. ARTHUR J. BEDELL, Albany, N. Y.: The patient to whom Dr. McGavic referred was presented at the 1921 session of the Academy of Ophthalmology and Otolaryngology. She was 52 years old and had noticed a redness of her right eye for one year before she came under observation March 5, 1920. She had a pericorneal mass 14 mm. wide and 5 mm. thick. The conjunctiva was incised; the growth was removed and found to be a lymphoma.

The eye was quiet when examined five months later, but one month after that there was a 7 by 5 mm. mass above the cornea and a 4 by 5 mm. one below. These continued to grow until they were larger than the primary tumor. On Sept. 12, 1922 radium was applied directly to the conjunctiva and there was complete disappearance of both masses. There was a recurrence July 19, 1927; an elevated, smooth, pink ridge was present about the inferior nasal limbus. In two years this grew to the size of the original tumor. Radium was again used, and the tumor vanished. The patient remained free from annoyance until 1933, when a small subconjunctival mass developed in the upper nasal quadrant at the limbus. She was not seen for two years.

On her return in 1935, the right eye was 9 mm. more prominent than the left and motion to the temporal side was limited. The vessels of the upper eyelid were distended. An oval mass about 20 mm. long and 6 mm. wide was outlined in the superior, temporal portion of the orbit, but the deep border could not be palpated. The cornea was almost completely encircled by an elevated, red, smooth solid mass in some places 10 mm. wide and in others, particularly in the lower part of the orbit, narrower and nodular. The left orbit was involved for the first time. An oval tumor 18 mm. long was beneath the lid but not attached to the globe. There were, however, some firm adherent, subperiosteal nodules.

On May 16 there was no roentgenographic evidence of invasion in the bony structure of the orbits. The accessory sinuses were clear, and there was no evidence of intracranial disease.

The patient received two roentgen ray treatments, the first on June 3, with 600 r to both orbits, and the second on August 13, with 480 r to both orbits.

By September 30 there was only a mere trace of conjunctival congestion, for the tumors had all disappeared. When next examined, Oct. 7, 1936, the patient reported that erythema nodosa extending from her knees to her ankles had necessitated rest in bed for three weeks. The eyeballs and orbits were clear, but she complained of her nose. There was a large tumefaction of the right middle turbinate.

She was not seen for another year, when she stated that she had had several nasal hemorrhages and as a result had been confined to bed all summer because of a profound anemia. There were no orbital recurrences. The right lens was completely opaque.

On May 6, 1939 I removed the cataract in capsule. Recovery was uneventful.

The patient died from an uncontrollable intestinal hemorrhage July 14, 1939, and unfortunately no autopsy was permitted.

This unusual case of recurring tumors so radiosensitive that they were clinically completely destroyed by either radium or roentgen rays was followed for nineteen years. The patient had a successful cataract extraction on the side of the original and most persistent involvement, and the fundus was found clear. In the left fundus there had been several retinal hemorrhages terminating in retinitis proliferans. Shortly before her death she had severe anemia and myocarditis.

The second case was recorded in the article referred to by Dr. McGavic.

In the third case, a 67 year old man was first seen in 1930, when his eyes were normal. In 1937 he had what was diagnosed as lymphosarcoma of the mediastinum and neck. This responded to roentgen ray treatment. A year later his prostate was removed and its condition reported nonmalignant. In 1939 a soft, gelatinous mass developed in the outer part of the upper cul-de-sac of the left eye. He was advised to have roentgen ray treatments, and resolution started after the second.

Subsequently the growth entirely disappeared. In 1940 a similar mass appeared in the right eye and there were recurrences in the neck, axilla and groin, and, although these vanished after roentgen ray treatment, he succumbed early in 1940.

DR. JOHN S. MCGAVIC, New York: Dr. Benedict has stated that he also has encountered difficulty in the diagnosis, even histologically. He mentioned Mikulicz' disease, lymphoma involving the salivary and lacrimal glands. Recently I saw a patient with this syndrome due to tuberculosis; irradiation was stopped after the biopsy and I believe the patient was saved some ocular trouble. I certainly agree with Dr. Benedict that a pseudotumor should present sufficient histologic characteristics so that it need not be confused with a lymphoma. The difficulty lies in getting the report from the general pathologist rather than from an ophthalmic pathologist, because the general pathologist does not always think about pseudotumors (granulomas).

Dr. Rones has thoughtfully gone over the Army Medical Museum specimens, which I have also seen; I think the lymphatic tumor registry is valuable.

Dr. Bedell reported the first conjunctival lymphoma in this country. I think it is fitting that after following the case for nineteen years he should make a subsequent report. Such follow-up is rare, indeed.

EPINEPHRINE MYDRIASIS

LEO HESS, M.D.
BOSTON

Instillation of epinephrine hydrochloride solution (1:1,000) into the conjunctiva of a normal person will not produce any change in the size of the pupil except a dilatation of 2 to 4 mm. Many years ago Loewi [1] noticed that in dogs instillation of this drug after removal of the pancreas gave rise to a distinct, sometimes maximum, mydriasis. Sometimes the eyeball protruded and the eyelids could not meet. Undoubtedly, these signs pointed to an increased activity of the sympathetic fibers innervating the dilator pupillae, the tarsalis superior and inferior and the orbitalis muscles. It was interesting that in cases of severe diabetes with acidotic coma, Loewi could detect the same mydriatic effect after the instillation of epinephrine hydrochloride. As far as my experience goes, I observed a Loewi reaction so frequently in comatose diabetic patients during my work in the clinics of Chvostek and Noorden (mostly in the era before insulin treatment was instituted, but in the insulin era too) that it appeared to be almost a characteristic sign of diabetic coma. In coma associated with hypoglycemia, uremia, apoplexy and alcoholic intoxication, on the other hand, it is never present. Later, the same reaction was noticed in patients with hyperthyroidism, in patients with chronic hypertensive disease of the kidneys (with which, in my opinion, some enlargement of the thyroid gland is not rare), in certain patients with glaucoma and, interestingly enough, according to the important studies of Schoenberg,[2] in 50 per cent of descendants of patients with glaucoma.

It might therefore be of some interest—from the scientific as well as from the diagnostic standpoint—to elucidate the mechanism of this reaction.

In accordance with the modern conception of the structure of the sympathetic nervous system, the pupil-dilating pathways are built up by three neurons.

The first, or central, neuron is supposed to start from the subthalamic corpus luysi. The fibers run from there through the tegmentum of the brain stem and down the spine to the eighth cervical and the first thoracic vertebrae and terminate in certain ganglion cells of the lateral horn at this level. From these cells the pupillary fibers run their course along the first thoracic root into the first intercostal nerve and through the ramus communicans into the sympathetic trunk. After passing the inferior and the middle cervical ganglion, the fibers find their synapse in the superior cervical ganglion (second, or so-called preganglionic, neuron). From the superior cervical ganglion arise the so-called postganglionic fibers (third, or postganglionic, neuron), and they are conveyed into the cranium with the internal carotid artery. They form at the inner side of this artery the cavernous plexus, from which they are transmitted to the dilator muscle of the iris, partially in the long ciliary nerves and partially in the short ciliary nerves, without being interrupted in the ciliary ganglion. On the basis of clinical experience it is safe to state that it is interruption of the third neuron (excision of the superior cervical ganglion, severing of the fibers surrounding the internal carotid artery) that results invariably in maximum mydriasis after the instillation of epinephrine hydro-

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Dr. Hess was formerly professor of Medicine and Neurology at the University of Vienna.

1. Loewi, O.: Wien. klin. Wchnschr. **20**:1, 1907; Arch. f. exper. Path. u. Pharmakol. **59**:83, 1908.

2. Schoenberg, M.: Tr. Am. Ophth. Soc. **22**:53, 1924.

chloride. Interruption of the central or of the preganglionic neuron does not give rise to distinct mydriasis. The site of the lesion in all surgical cases in which epinephrine hydrochloride produces distinct mydriasis can be assumed to be in the area between the superior cervical ganglion and the radial, dilating fibers of the iris.

However, it is not surgical measures alone that are followed by epinephrine mydriasis. Mechanical pressure of an enlarged thyroid on the sympathetic fibers has the same effect. Goodman and Gilman [3] stated that sensitization of the sympathetic structures by increased production of thyroxin may likewise result in epinephrine mydriasis. But this statement needs further investigation. In contradistinction, cocaine mydriasis is greatest after interruption of the first, or central, neuron; it cannot be demonstrated either after interruption of the postganglionic fibers or after destruction of the second neuron. Moderate mydriasis is ordinarily present after instillation of a 1 per cent solution, because of its action on the peripheral sympathetic nerve endings.

In any event, the Loewi reaction is indicative of a disturbance of the third neuron in the pupil-dilating pathway. It is true that the iris of some animals quickly responds to epinephrine with mydriasis after denervation. However, it would hardly be reasonable to compare this reaction to the complex conditions of the human body in such diseases as diabetes, hyperthyroidism and nephritis.

In rare cases of glaucoma, one finds in addition to the fixed, dilated iris in the affected eye, a Loewi reaction in the fellow organ and a high resistance of the dilated iris to miotic drugs. In these cases one is probably dealing with a sympathicotonic condition (Eppinger and Hess [4]).

COMMENT

Epinephrine mydriasis, in the light of present knowledge, is a sign of some lesion of the third neuron in the sympathetic pathway of the pupil. In surgical cases it can be accounted for by a lesion in the area between the superior cervical ganglion and the iris. In glaucoma it is probably connected with sympathicotonia. In diabetic coma, hyperthyroidism and nephritis it is probably due to a functional toxic disturbance of the third neuron. In normal persons the activity of the third neuron is to some extent blocked by the superior cervical ganglion. After elimination of the blockade, the response of this neuron to the sympathomimetic drug is undisturbed and Loewi's reaction occurs. This reaction can prove useful in the differential diagnosis of comatose conditions.

Epinephrine mydriasis in dogs after removal of the pancreas will be discussed in another paper.

15 Kenwood Street, Brookline, Mass.

3. Goodman, L., and Gilman, A.: The Pharmacological Basis of Therapeutics, New York, The Macmillan Company, 1941, p. 410.
4. Eppinger, H., and Hess, L.: Ztschr. f. klin. Med. **68**:69, 1905.

PRIMARY TUBERCULOSIS OF THE CONJUNCTIVA

OLGA SITCHEVSKA, M.D.
AND
MARGARET SEDAM, M.D.
NEW YORK

Tuberculosis of the visual apparatus is not frequent and is apparently to a certain degree antagonistic to pulmonary tuberculosis; i. e., the eye is rarely affected in tuberculosis of the lungs, and vice versa.[1] Primary tuberculosis of the conjunctiva, or the appearance of tuberculosis in the conjunctiva in a previously uninfected organism, is uncommon. It occurs in early life, before tuberculous allergy has developed, according to Duke-Elder.[2] From the infected conjunctiva, the bacilli enter the regional lymph nodes which drain the conjunctiva, and the primary complex after Ranke of the first stage of tuberculosis [1] is formed.

Koester [3] was the first to report a case of tuberculosis of the human conjunctiva, in 1873, and Sattler,[4] in 1874, was next, describing a tuberculous ulceration of the conjunctiva. Parinaud,[5] in 1884, made a contribution concerning the diagnostic value of experimental inoculation of the infected conjunctival tissue into the anterior chamber of the rabbit's eye.

CASE INCIDENCE

Only isolated cases of tuberculosis of the conjunctiva have been reported in this country, by Coover,[6] Cohen,[7] Thompson [8] and McKenzie.[9] Bordley [10] stated that no patients with tuberculosis of the conjunctiva were seen at the Baltimore Eye, Ear and Throat Charity Hospital among 41,730 treated patients. Benalioua [11] reported on only 2 such patients, whom he had observed among 60,000 patients with ocular diseases in Oran, Algeria. In 1938 he collected reports on 181 patients with tuberculosis of the conjunctiva; 62 of these had primary tuberculosis. In twenty years Burchell [12] had not encountered a patient with tuberculosis of the conjunctiva at the New York Eye and Ear Infirmary, where the average annual admissions of new eye patients is about 30,000. Ivanov [13] stated that only 2 such patients were seen in

Read before the New York Academy of Medicine, Section of Ophthalmology, April 18, 1942. A discussion of this paper appeared in the December 1942 issue of the ARCHIVES, page 1115.

1. Sergievsky, L.: Tuberculosis and the Eye: Collective Papers Dedicated to M. Averbach, Moscow, State Publishers, 1935, p. 422.
2. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 2, p. 1476.
3. Koester, cited by Eyre.[15]
4. Sattler, H.: Tubercular Ulceration of the Conjunctiva, Irish Hosp. Gaz. **2**:101, 1874.
5. Parinaud, H.: Tuberculose primitive de la conjonctive; valeur des inoculations expérimentales pratiquées dans la chambre antérieure de l'oeil, Gaz. hebd. de méd. **21**:398, 1884.
6. Coover, D.: Tuberculosis of the Conjunctiva, Am. J. Ophth. **3**:206, 1920.
7. Cohen, M.: Tuberculosis of the Conjunctiva, Arch. Ophth. **48**:96, 1919.
8. Thompson, J.: Primary Tuberculosis of the Conjunctiva, Ann. Ophth. **15**:76, 1906.
9. McKenzie, W. H.: Tuberculosis of the Conjunctiva, Am. J. Ophth. **22**:744, 1939.
10. Bordley, J.: Tuberculosis of the Conjunctiva, Ophth. Rec. **11**:368, 1902.
11. Benalioua: Le primo-infection tuberculeuse de la conjonctive, Ann. d'ocul. **175**:746, 1938.
12. Burchell, E.: Personal communication to the author.
13. Ivanov, N.: Tuberculosis of the Conjunctiva, Vestnik oftal. **14**:24, 1939.

the Moscow Eye Clinic in 1935 among 94,000 patients. Samuelson [14] observed during the years from 1915 to 1934 7 patients with tuberculosis of the conjunctiva among 181,000 patients at the ophthalmic clinic of the Seraphimer Hospital, in Stockholm, and only 3 of these had primary infection of the conjunctiva. Eyre,[15] on the other hand, stated that he encountered patients with tuberculosis of the conjunctiva at the rate of 1 among 2,700 patients with ophthalmic disorders; in 1912 he collected reports on 206 patients from whose conjunctivas the tubercle bacillus was isolated. Blegvad [16] had encountered 40 patients with primary tuberculosis of the conjunctiva during the years 1909 to 1934 in the Finsen Institute, in Copenhagen. He stated the belief that this frequent occurrence of tuberculosis of the conjunctiva was due to the prevalence of tuberculosis in cattle in Denmark. According to Saemisch,[17] the frequency of tuberculosis of the conjunctiva as compared with that of other ocular diseases varies from 1 : 1,300 to 1 : 30,000.

MODE OF INFECTION

There are three possible pathways of infection of the conjunctiva: 1. Exogeneous, or primary, infection is direct inoculation of the conjunctiva by tubercle bacilli which enter the conjunctival sac from the outside world. 2. Endogeneous. or secondary, infection is invasion of the conjunctiva by tubercle bacilli brought by the blood stream from a tuberculous focus eleswhere in the body (e. g. the lungs), or by metastasis. Meisner [18] called this form of lesion a superinfection. In it there is no tendency for the infection to spread along the lymph vessels and nodes. 3. Finally, the conjunctiva may be infected by continuity from an adjacent part in which there is a tuberculous process, for example from the skin of the face in lupus or from the mucous membrane of the nose via the tear passages.

The exogenous pathway has aroused a considerable amount of controversy. Some experimenters have maintained that a healthy conjunctiva cannot be infected. Langhans [19] in 1867 and Haensel [20] in 1879 produced specific inflammation of the conjunctiva of the rabbit by inoculation of pure culture of tubercle bacilli. Valude [21] stated the belief that the tears do not favor the growth of tubercle bacilli, and Lagrange [22] maintained that a conjunctival lesion can be produced only by subconjunctival injections of tubercle bacilli. Bruckner's [23] experimental study in 1929, however, showed that an intact conjunctiva can be permeable to tubercle bacilli. In the course of chronic conjunctivitis in guinea pigs, the phagocytes ingested the tubercle bacilli and dragged them into the subepithelial tissue, and thus tuberculous granulation tissue developed. That the immunobiologic condition of the organism plays an important role during the infection was demonstrated by

14. Samuelson, D.: Primary Tuberculosis of the Conjunctiva, Arch. Ophth. **15**:975 (June) 1936.

15. Eyre, J. D.: Tuberculosis of the Conjunctiva, Lancet **1**:1319, 1912.

16. Blegvad, O.: Fortgezetste Untersuchungen über die conjunctival Tuberculose, Acta ophth. **14**:200, 1936.

17. Saemisch, T.: Tuberculose der Bindehaut, in Graefe, A., and Saemisch, T.: Handbuch der gesamten Augenheilkunde, ed. 2, Leipzig, W. Engelmann, 1909-1911, vol. 5, p. 484.

18. Meisner, W.: Bindehaut und Tuberculose, München. med. Wchnschr. **80**:677, 1933.

19. Langhans, T., cited by Igersheimer.[24]

20. Haensel, P., cited by Igersheimer.[24]

21. Valude, cited by Saemisch.[17]

22. Lagrange, N.: Innoculation de la tuberculose et superinfection experimentale par la voie conjunctivale, Ann. d'ocul. **160**:849, 1923.

23. Bruckner, Z.: Étude histolgique de la perméabilité de la conjonctive aux bacilles tuberculeux, Ann. d'ocul. **166**:804, 1929.

Igersheimer.[24] He obtained a different reaction with tuberculous and with nontuberculous animals. Fifty-four tuberculous guinea pigs inoculated with a pure culture of human or bovine tubercle bacilli showed no swelling of the regional lymph nodes, while in healthy guinea pigs a conjunctival lesion and regional lymphadenitis usually developed. Igersheimer thus stated that a primary infection of the conjunctiva is possible and that whenever the preauricular and other regional glands are inflamed the primary nature of the lesion is indicated. Morax [25a] was the first, in 1906, to establish the primary nature of infection of the conjunctiva accompanied by a regional adenopathy; he called this combination the conjunctival-preauricular complex. This point of view was supported by Saemisch [17] and Magitot.[26] The tuberculin test is a means of deciding whether one is dealing with a primary infection, but the test must be done as early as the first few weeks, i. e., before tuberculous allergy has developed, according to Duke-Elder.[2] Unfortunately there is rarely an opportunity to do a tuberculin test during this period, as the patient usually presents himself to the physician when the symptoms are far advanced and he is allergic.

There are several modes of infection (Eyre): (1) contact with tuberculous relatives or playmates, (2) conveyance from similar sources by soiled handkerchiefs or towels and (3) the lodging of dried particles of dust carrying the bacilli in the conjunctival sac, where they produce a small abrasion by their sharp angles. In favor of the third type is the fact that tuberculous ulcers [27] frequently begin in the subtarsal sulcus, where foreign bodies are apt to lodge. The reports of Vancea,[28] Takagi [29] and Bordley [10] of primary tuberculosis of the conjunctiva developing after injury of the conjunctiva support this view. Lawson,[30] Blegvad,[16] Birch-Hirschfeld and Kausmann [31] have observed tuberculosis of the conjunctiva in patients who milked cows which had tuberculosis; the infection may have been carried with the hands or the udder may have been touched by the eye. Tubercle bacilli of the bovine type were present in the cultures of these patients. Tchemolossov [32] reported that tuberculosis of the conjunctiva developed in a 37 year old man because a woman with active tuberculosis of the lungs tried to remove a foreign body from his conjunctiva by licking it out with her tongue. A still stranger case was reported by Stutzer.[33] Tuberculosis of the conjunctiva developed in a man after he had been bitten in the eye by a dog which had eaten the placenta of a tuberculous cow.

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24. Igersheimer, J.: Experimentelle und klinische Untersuchungen zur Bindehaut Tuberculose, Klin. Monatsbl. f. Augenh. **69**:226, 1922.

25. (*a*) Morax, V.: La tuberculose de la conjonctive, in Lagrange, F., and Valude, E.: Encyclopédie française d'ophtalmologie, Paris, O. Doin, 1906, p. 782. (*b*) Morax, V., and Rist, E.: Pronostic de l'infection tuberculeuse primitive de la conjonctive, Bull. Acad. de méd. **113**: 252, 1935.

26. Magitot, A.: Primo-infection tuberculeuse de la conjonctive, Bull. Soc. d'opht. de Paris **6**:380, 1937.

27. Fuchs, E.: Text Book of Ophthalmology, ed. 8, Philadelphia, J. B. Lippincott Company, 1924, p. 495.

28. Vancea, P.: La tuberculosi primitiva post traumatica della conguintiva, Ann. di ottal. e clin. ocul. **60**:490, 1932.

29. Takagi, T.: Ueber einen Fall von epibulbar Tuberculosis, Zentralbl. f. d. ges. Ophth. **37**:344, 1936.

30. Lawson, A.: Diagnosis and Treatment of Ocular Tuberculosis, Tr. Ophth. Soc. U. Kingdom **49**:45, 1929.

31. Birch-Hirschfeld, A., and Kausmann, W.: Drei Fälle von conjunctival Tuberculose, Klin. Monatsbl. f. Augenh. **38**:634, 1900.

32. Tchemolossov, M.: Tuberculosis of the Conjunctiva, Russk. oftal. j. **23**:619, 1900.

33. Stutzer: Beitr. z. pract. Augenh., 1898, p. 10.

The age limits within which tuberculosis of the conjunctiva occurs vary with different authors. The outstanding feature is that the disease appears chiefly during the early years of life. Lundsgaard [34] called tuberculosis of the conjunctiva a juvenile disease because 25 patients he had observed were all under 20. Eyre [15] gave the upper age limit as 30 years and stated that the disease occurred most frequently at the age of puberty. In one third of his patients it was observed within the first decade of life. Villard [35] stated that in 72 per cent of the patients tuberculosis of the conjunctiva occurred before the age of 20. The lower limit has been gvien as 6 months and the upper as 63 and 76 years (Motolese,[36] Neame [37]).

The various clinical forms of tuberculosis of the conjunctiva were divided by Sattler [4] and Eyre [15] into five classic types, which were described in a masterly way by the latter. These are: (1) the ulcerative type, (2) the nodular type, (3) hypertrophic granulation, (4) lupus and (5) the pedunculated tumor. Eyre, among his 206 collected cases, found that 80 were instances of hypertrophic granulation; i. e., this is the most frequent type. It is characterized by massive red hypertrophied papillae scattered over the tarsal conjunctiva, with mushroom-shaped masses of granulation tissue which bear a close resemblance to the comb of a fowl. They frequently are derived from the fornix and produce edema and swelling of the lid, with a mucopurulent discharge and enlarged preauricular or submaxillary glands. Eyre stated the belief that the presence of type 1 or type 3 indicates the inoculation of a distinctly susceptible person with numerous virulent bacilli, while type 2 and type 5 comprise infection of a resistant person with a small number of attenuated bacilli. The various types, however, are frequently combined, and many infections present an anomalous, individualistic appearance, conforming to no type at all.

The clinical signs and symptoms are as follows: The complaints are trivial. The patient seeks medical advice because of drooping of the lid or swelling of the cheek. Ptosis and swelling of the lid and of the preauricular gland on the same side of the face frequently appear simultaneously; if the glandular swelling is considerable, the face is deformed, and frequently the cervical and submaxillary glands are involved. Preauricular lymphadenitis is often noticed prior to the swelling of the lid. The involvement of the preauricular and other regional lymph nodes which drain the conjunctiva is considered to be the most valuable symptom of primary tuberculosis of the conjunctiva. Saemisch,[17] Igersheimer [24] and Morax [25] stated that in unilateral tuberculosis of the conjunctiva the involvement of the regional lymph nodes always indicates a primary infection and that whenever there is no involvement of these glands the infection of the conjunctiva is secondary. The adenopathy persists longer than the conjunctival granulations. In only about one fourth of the cases has it been possible to find tubercle bacilli in the excised conjunctival tissue, and they have been found in the preauricular gland as frequently as in the conjunctiva (Samuelson). The glands are frequently painful and suppurate readily.

The conjunctiva of both lids is affected most frequently; Eyre gave the ratio as 2:1 in favor of the upper lid; the fornix is affected in about 8 per cent of the cases according to Villard,[35] and the bulbar conjunctiva is involved infrequently.

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34. Lundsgaard, K.: Tuberculosis Conjunctivae: The Eventual Fate of the Patient, Acta ophth. **1**:39, 1924.

35. Villard, H.: La tuberculose de la conjonctive, Ann. d'ocul. **134**:87, 1905.

36. Motolese, A.: Contributo allo studio della tuberculosi della conguinctiva, Boll. d'ocul. **16**:895, 1937.

37. Neame, H.: Conjunctival Tuberculosis, Tr. Ophth. Soc. U. Kingdom **34**:76, 1934.

As a rule only one eye is affected, and the only description of a case of bilateral tuberculosis of the conjunctiva found in the literature was that of Tita.[38] A girl 9 years old had ulcers in the conjunctiva of both upper lids. The biopsy showed Koch's bacilli and giant cells in the lesion.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of tuberculosis of the conjunctiva is frequently difficult and confusing. Many ophthalmologists have associated for years unilateral conjunctival lesions accompanied with lymphadenitis with Parinaud's conjunctivitis.

In 1889 Parinaud and Galezowski[39] described before the Ophthalmologic Society of Paris 3 cases of unilateral granulation of the conjunctiva with enlargement and suppuration of the preauricular and cervical glands; the conjunctiva was the seat of red and yellow vegetations, which were semitransparent at first and became opaque at a later stage. Parinaud considered the infection to be the result of an unknown organism derived from animals, as it was met with in butchers and in others who dealt with animals. He named it *conjunctivite infectieuse d'origine animale*. It has been made clear by numerous observers that Parinaud's conjunctivitis is not a definite disease with a uniform picture, but merely a syndrome of signs and symptoms, and it is regarded as certain that the infection is not derived from diseased animals. Verhoeff[40] stated that what was known as Parinaud's conjunctivitis is a clinical and a histologic entity due to infection with the leptothrix. Verhoeff demonstrated the presence of leptothrices in the conjunctival lesion in 1913 by a special method of staining and by fixing the excised tissue in Zenker's fluid. These organisms were observed in 45 cases in twenty-eight years in the Massachusetts Eye and Ear Infirmary. In 1933 Verhoeff and King[41] isolated them in 3 cases in pure cultures on an artificial medium. Pascheff,[42] on the other hand, observed 3 cases of abscesses and necrosis of the conjunctiva in which guinea pigs infected with matter from the abscesses died in a few days. He isolated Microbacillus necroticans from these abscesses and named the disease "conjunctivitis necroticans infectiosa." Ochapovskaya[43] stated that Parinaud's conjunctivitis is not an independent nosologic unit and that it can manifest itself grossly in association with tuberculosis, syphilis, tularemia and other infections of undetermined causation. She reported 2 cases. In one of these the diagnosis was Parinaud's conjunctivitis, but histologic examination proved the condition to be tuberculosis, and in the second case tuberculous tissue was not found, although the clinical picture was characteristic of tuberculosis of the conjunctiva. Van der Straeten and Applemans[44] described a case in which the clinical course was that of follicular conjunctivitis, and only guinea pig inoculation and a biopsy established the diagnosis of tuberculosis of the conjunctiva.

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38. Tita, C.: Tuberculosi palpebro-conguintivale, Ann. di ottal. e clin. ocul. **67**:871, 1939.

39. Parinaud and Galezowski: Conjonctivite infectieuse transmise par les animals, Ann. d'ocul. **101**:252, 1889.

40. Verhoeff, F.: Lepthotricosis Conjunctivae (Parinaud's Conjunctivitis), Arch. Ophth. **42**:395, 1913.

41. Verhoeff, F., and King, M.: Leptothricosis Conjunctivae (Parinaud's Conjunctivitis), Arch. Ophth. **9**:701 (May) 1933.

42. Pascheff, C.: The Differential Diagnosis Between Parinaud's Conjunctivitis and Conjunctivitis Necroticans Infectiosa, Brit. J. Ophth. **8**:25, 1924.

43. Ochapovskaya, N.: Parinaud's Syndrome and Tuberculosis of the Conjunctiva, Vestnik oftal. **18**:278, 1941.

44. van der Straeten, M., and Applemans: La conjunctivite tuberculeuse, Bull. Soc. belge d'opht., 1936, no. 72, p. 15.

The etiologic problem of the glandular syndrome is immense. Tularemia has recently aroused much interest among ophthalmologists, and because it is so much more prevalent in the United States than anywhere else in the world its diagnosis calls for special attention. According to the statistics of the United States Public Health Service,[45] 8,137 cases of human tularemia have been reported in this country up to 1937. The conjunctiva was the primary seat of infection in 68 cases, and in 52 of these the infection was transmitted by the hands while the patient was dressing rabbits. Hurst [45] in 1938 described a series of 23 cases of unilateral conjunctivitis with vegetative growth and with swelling of one or more regional lymphatic glands. A histologic study was made in 12 cases. In 17 cases no causative organism was demonstrated; no clinical difference was noted between cases in which the leptothrix was found and cases in which it could not be demonstrated. In 2 cases oculoglandular tularemia was differentiated from Parinaud's conjunctivitis, and Hurst stressed the point that these conditions "are separate disease entities."

Sanford Gifford in 1934 [46] and again in 1938 [47] suggested most valuable points of differentiation of the diseases which are associated with unilateral adenopathy and conjunctival granulations. He stated that the conjunctivoglandular syndrome of Parinaud should be divided into three etiologically distinct entities, namely, tuberculosis of the conjunctiva, leptothricosis of the conjunctiva and the oculoglandular form of tularemia. In every case there should be an examination of excised tissue for acid-fast bacilli, with guinea pig inoculations whenever possible. An examination of excised tissue fixed in Zenker's fluid and stained by Verhoeff's modified Gram method will establish the diagnosis of leptothricosis of the conjunctiva. In the oculoglandular form of tularemia the systemic symptoms are severe, an agglutination test of the patient's serum for Bacillus tularensis usually gives positive results in the second or third week and a carefully taken history reveals contact with rabbits or squirrels.

Acute trachoma, vernal catarrh, chancre of the conjunctiva and epithelioma are to be differentiated from tuberculosis of the conjunctiva. A biopsy of the conjunctiva is important, and should reveal either the presence of tubercle bacilli or specific cytologic changes of tuberculosis. Guinea pig inoculations always make the diagnosis certain.

COURSE

In some cases the course is benign and the infection clears up spontaneously or responds well to treatment, while in others the course is protracted. In some cases tuberculosis of the conjunctiva has led to general phthisis of the lungs and death. Derer [48] reported a case of tuberculosis of the conjunctiva in a woman aged 28. The process rapidly involved the bulbar conjunctiva. A few weeks later tuberculous pharyngitis was followed by laryngitis; in another four weeks a violent hemoptysis led to death. Licheri [49] reported on a 20 year old girl in whom pleurisy developed eight months after primary tuberculosis of the conjunctiva appeared. She died three years later of pulmonary tuberculosis. In Ivanov's [50]

45. Hurst, V.: Oculo-Glandular Diseases with Special Reference to Tularemia and Parinaud's Conjunctivitis, Tr. Am. Acad. Ophth. **43**:363, 1938.

46. Gifford, S., and Dillon, E.: The Conjunctivo-Glandular Syndrome of Parinaud: Report of a Case Showing a Thread Mold in Sections, Arch. Ophth. **12**:518 (Oct.) 1934.

47. Gifford, S.: Oculo-Glandular Diseases, Tr. Am. Acad. Ophth. **43**:371, 1938.

48. Derer, cited by Duke-Elder.[2]

49. Licheri, G.: A Case of Primary Tuberculosis of the Conjunctiva, Lettura oftal. **15**: 403, 1938; abstracted, Am. J. Ophth. **35**:495, 1942.

50. Ivanov, N.: Tuberculosis of the Conjunctiva, Vestnik oftal. **14**:25, 1939.

case the conjunctival lesion was so severe that the cornea became involved, and the final result was atrophy of the eyeball. Fortunately these are isolated instances, while in the majority of the reported cases the process was rather benign. Morax [25] followed up 7 young patients for years. In all of these the conjunctival tuberculosis terminated in cicatrization. Similar observations were made by Cantonnet, and Genevrier,[51] Troisier,[52] François,[53] van der Straeten and Applemans,[44] Goutela and Offeret,[54] Pierret and Lefebyre [55] and Blumenfeld.[56]

TREATMENT

Excision or curettage of the conjunctival lesion with subsequent cauterization of the wound either with the galvanocautery or with a solution of 50 per cent lactic acid is considered the method of choice; it is particularly recommended if the lesion is not so large that extensive scarring or deformity of the lid will be produced.

The Scandinavian physicians claim that the Finsen treatment, or local use of ultraviolet light, gives the best possible cosmetic results, as the scar of the conjunctiva remains smooth. Samuelson,[14] who observed 3 cases of primary tuberculosis of the conjunctiva at the ophthalmic clinic of the Seraphimer Hospital, in Stockholm, and Lundsgaard [34] and Blegvad [16] reported favorably on this treatment. The French ophthalmologists obtained favorable results in treating tuberculosis of the conjunctiva with injections of a methylic tuberculosis antigen (a methyl alcohol extract of tubercle bacilli treated with acetone). This treatment was used widely in Paris (Cantonnet and Genevrier,[51] François,[53] van der Straeten and Applemans,[44] Goutela and Offeret [54] and Djacos[57]).

Roentgen ray treatment to the suppurated and fistulized lymph nodes was found to be effective by most writers. Denti [58] and Matzei [59] applied the rays also to the conjunctival lesion and obtained good results in 3 cases and in 2 cases, respectively. The local application of 20 per cent iodoform ointment is considered efficacious by some authors. Eyre and Williamson-Noble [60] advocated the use of injections of old tuberculin, while Duke-Elder [2] stated that "in conjunctival lesions tuberculin does not usually give good results."

It seems as though the less one does the better off the patient is. Magitot [26] reported a case in which the local treatment gave disastrous results. A girl aged 5 had a number of ulcerated follicles on the tarsal conjunctiva of the right eye. Magitot applied diathermocoagulation, and a severe reaction followed; the cornea was involved and the eyeball eventually had to be eviscerated. He therefore advised the use of a fine cautery point in order not to cause a severe reaction. General

51. Cantonnet, A., and Genevrier, R.: Tuberculose conjonctivale de primo-infection chez un adolescent, Rev. gén. de clin. et de thérap. **52**:369, 1938.

52. Troisier, J., and Renard, G.: Primo infection tuberculeuse de la conjonctive, Ann. d'ocul. **175**:794, 1938.

53. François, J.: Étude sur la conjonctivite tuberculeuse du type folliculaire, Bull. Soc. belge d'opht., 1934, no. 68, p. 46.

54. Goutela and Offeret: Un cas de primo inoculation tuberculeuse de la conjonctivite, Ann. d'ocul. **173**:907, 1936.

55. Pierret, R., and Lefebyre, G.: Un cas de primo-infection tuberculeuse au niveau de la conjonctive palpebrale, Presse méd. **45**:1250, 1937.

56. Blumenfeld, N.: Tuberculosis of the Conjunctiva, Vestnik oftal. **18**:203, 1941.

57. Djacos, C.: Un cas de tuberculose conjonctivale guérie par l'antigène méthylique, Bull. Soc. d'opht. de Paris, 1936, p. 542.

58. Denti, A.: Note sulla tuberculosi della conguintiva, Ann. di ottal. e clin. ocul. **60**: 88, 1932.

59. Matzei, A.: Sulla tuberculosi della conguintiva, Boll. d'ocul. **15**:820, 1939.

60. Williamson-Noble, F.: Tuberculin in Ophthalmology, Brit. J. Ophth. **16**:285, 1932.

hygienic measures, which will increase the resisting power of the organism—an abundance of fresh air, a generous diet and cod liver oil—go hand in hand with the local and surgical treatment.

REPORT OF A CASE

Michael A., 18 months old, was first seen at the ophthalmic clinic of the New York Infirmary for Women and Children on April 23, 1941. There was a history of the simultaneous appearance six weeks earlier of swelling of the left upper eyelid and of a lump on the left cheek in front of the ear. The child had been well until then. The examination revealed that he was well nourished. The face was deformed because of swelling of the left cheek and the left upper part of the neck. The left preauricular gland was the size of a walnut, was painful and soft and fluctuated in the center on palpation. There were a firm node below and behind the left side of the jaw and an enlarged, firm gland on the left side of the neck. The left upper lid was reddened, swollen and ptosed, especially on the temporal side; there was much mucopurulent discharge from the eye (fig. 1). On eversion of the upper lid (which was difficult) the palpebral conjunctiva was found to be hyperemic and thickened, containing follicles of various sizes; in some places the follicles were confluent and resem-

Fig. 1.—Photograph of the patient showing ptosis of the lid and swelling of the preauricular and cervical glands.

bled proliferations. One such granulation, the size of a pea, was located in the tarsal conjunctiva at the center of the outer third of the lid; it was covered with a yellow-gray membrane which bled easily when an attempt was made to wipe it away. The conjunctiva of the lower lid was congested, but no follicles were seen. The lacrimal gland was enlarged. The bulbar conjunctiva was also congested. The cornea was intact. The right eye appeared normal. The child was referred to the pediatric ward for study, diagnosis and treatment.

The preauricular gland was aspirated on the second day after admission, and acid-fast bacilli were discovered in the smear and culture, which fact revealed the tuberculous nature of the conjunctival lesion. The blood count showed some anemia. The hemoglobin content was 70 per cent, and there were 3,940,000 red cells and 17,000 white cells, with 59 per cent lymphocytes. No tuberculin test was done, because of the positive smear. Repeated roentgenograms of the lungs showed no infiltration of the parenchyma and no mediastinal adenopathy. A week later 1 cc. of greenish yellow purulent material was obtained by means of a second aspiration of the preauricular lymph node; the cervical node, which became soft, was also aspirated, and acid-fast bacilli was found there too. Roentgen ray therapy was administered to the preauricular gland and to the soft cervical node. Six small doses (75 to 100 roentgens) were given, with an interval of from four to five days, until there was no drainage and the inflammation and swelling of the gland were reduced

considerably. The general medical care involved a high vitamin diet and plenty of outdoor air and sunshine. Sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) was given internally as an aid toward overcoming secondary infection in the suppurating nodes. Local treatment of the eye consisted of application of warm compresses, instillation of 0.33 per cent solution of zinc sulfate and use of 1:5,000 mercury bichloride ointment, which was later replaced with 20 per cent iodoform ointment.

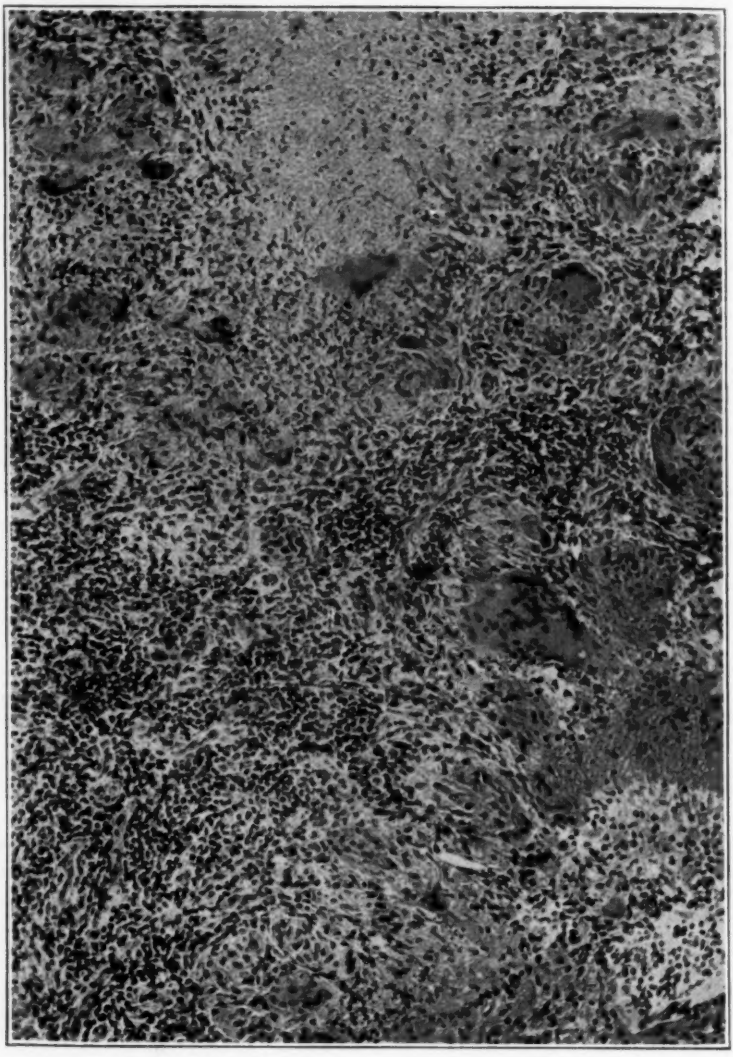

Fig. 2.—A photomicrograph of the excised conjunctival tissue showing tubercles, epithelioid and giant cells and lymphocytes.

The eye did not respond to the local treatment. An ulcer formed at the site of the granulation at the outer third of the tarsal conjunctiva; this had slightly elevated edges and a depressed, necrotic, grayish and yellow area in the center. Microscopic examination of ulcerous tissue taken eighteen days after the patient's admission to the hospital showed the lesion to be typically tuberculous, with tubercles, giant cells and caseation; staining revealed a limited number of tubercle bacilli. The pathologist's report was as follows: The specimen consisted of material from the palpebral conjunctiva. Approximately one fourth of the surface was covered by thin, stratified, squamous epithelium, which gradually

thinned out over the ulcerated surface. At this pole of the specimen, near the surface, several meibomian glands were present. The remainder of the surface showed vascular granulation tissue. The specimen was diffusely infiltrated with lymphocytes. Many typical miliary tubercles were seen, composed of rounded groups of epithelioid cells surrounded by wide zones of lymphocytes. Multinucleated giant cells of Langhan's type were observed in abundance. Some areas of caseation were noted; occasional small foci of fibrosis were

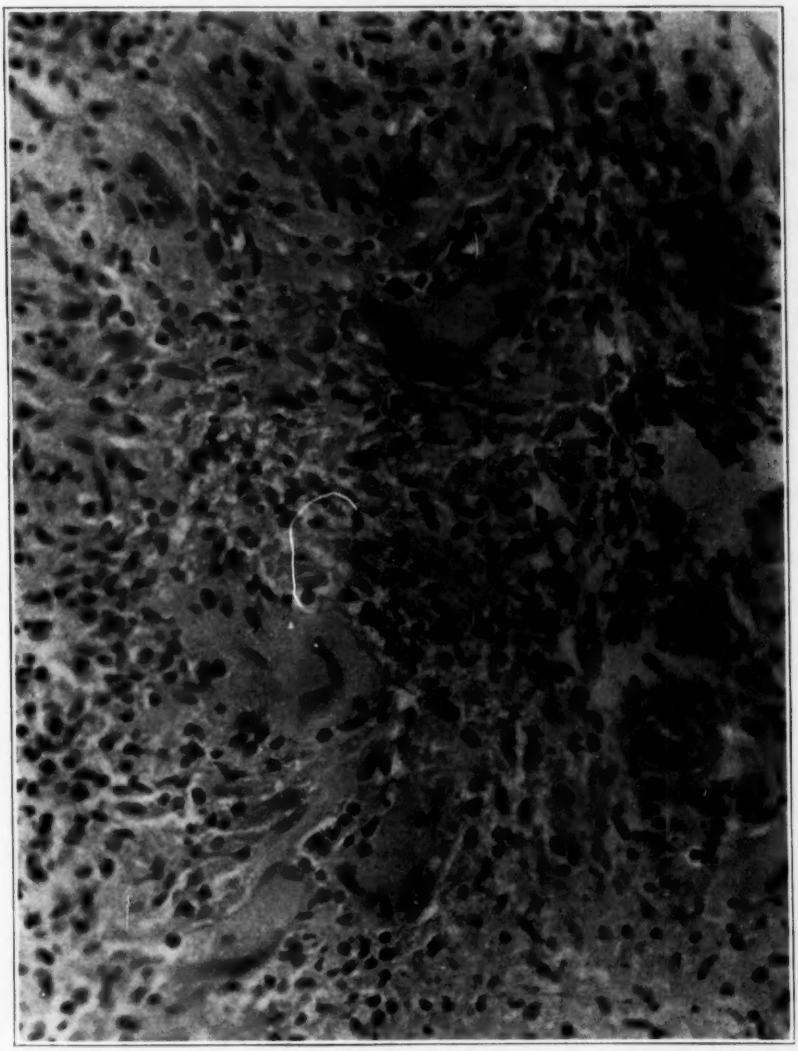

Fig. 3.—High power view of the section shown in figure 2.

seen. Some of the tubercles were conglomerate. Ziehl-Neelsen stain revealed numerous acid-fast organisms morphologically characteristic of tubercle bacilli.

The conjunctiva improved rapidly after the biopsy, and the child was discharged from the hospital, for convalescent care, about six weeks after admission. No animal inoculation was done, because of the definite diagnosis.

Michael was readmitted in September 1941, because the left submental node suppurated; on aspiration thick pus mixed with blood was obtained. Weekly roentgen ray treatments (100 r) were given to the suppurated gland. The left lid was slightly ptosed, and a few

small granulations were still present on the tarsal conjunctiva. A roentgenogram of the lungs gave no evidence of tuberculosis. The patient was discharged in four weeks to a convalescent home in a much improved condition. After one year of observation, in April 1942, he was in good health, the lid had healed completely (fig. 4) and there was only a fine scar left at the site from which the specimen for biopsy had been removed; an irregular-shaped scar was present at the site of the preauricular gland.

The source of the infection of this patient was obscure. There was no history of tuberculosis in the family; both parents were healthy and roentgenograms of their lungs showed no evidence of tuberculosis. The only possible source of infection was a friend of the family who had active tuberculosis of the lungs. Michael, however, was never in direct contact with the man, although he played frequently with his 5 year old daughter. In the latter, the Mantoux tuberculin test gave a positive reaction.

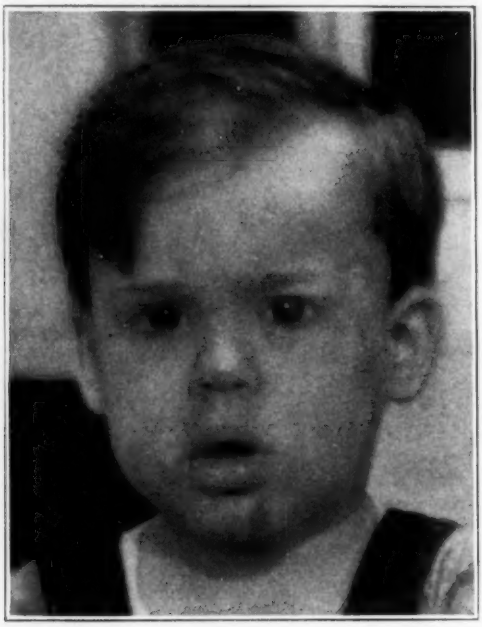

Fig. 4.—The child one year after admission to the hospital.

SUMMARY

A case of primary tuberculosis of the conjunctiva in a child 18 months old, with complete recovery, is reported. The diagnosis of primary tuberculosis was made because (1) a lesion was not present in any other organ of the body, (2) the process was unilateral and (3) there was involvement of the preauricular and other regional lymph nodes, which according to Ranke's classification is typical of the primary complex. The source of the infection was not certain. Tubercle bacilli were observed in the smear and culture of pus from the preauricular gland and in excised tissue from the conjunctival lesion. The taking of a specimen from the conjunctiva for biopsy apparently acted as a surgical therapeutic measure, as the eye improved rapidly after the biopsy. The suppurated lymph nodes responded well to aspiration and several fractional doses of roentgen ray treatments. The outcome proved to be favorable in this case, which is in accordance with the results obtained in the majority of cases reported in recent years.

30 Fifth Avenue.

KERATOCONJUNCTIVITIS SICCA

SANFORD R. GIFFORD, M.D.

IRVING PUNTENNEY, M.D.
AND
JOHN BELLOWS, M.D., PH.D.
CHICAGO

For about two years before the report of Bruce [1] which appeared in 1940 we had been interested in keratoconjunctivitis sicca and had collected data on a number of cases. Bruce covered the subject so well that the complete review which was in preparation seemed unnecessary, but the number of patients seen both before and after his report, in most of whom the disease was previously undiagnosed, and the fact that no other satisfactory study of the condition has appeared in the American literature prompt us to summarize certain facts learned from observation of these patients.

During the past four years, we have listed in our diagnosis file 49 patients as having evidence of deficient lacrimation. These patients may be divided into three groups:

Group I comprised 16 patients showing a lacrimal deficiency with moistening of less than 15 mm. on the Schirmer test after five minutes, but no corneal or associated changes.

Group II had 21 patients who showed fairly severe lacrimal deficiency with corneal and conjunctival changes of such a degree as to be visible only with the slit lamp, and as a rule no associated signs.

Group III comprised 12 patients showing the typical Sjögren syndrome, with almost no lacrimal secretion on Schirmer's test, marked corneal and conjunctival changes, and one or more of the extraocular signs of that syndrome, usually a deficiency of salivary secretion.

There were, in addition, 1 patient with pemphigus, 4 with neuroparalytic keratitis, 2 with superficial punctate keratitis and 2 with unilateral lacrimal deficiency due to removal of tumors involving the lacrimal apparatus.

Of group I it may be said that all the patients complained of ocular irritation which was unexplained by other findings. Some obtained relief from the use of a substitute for tears, while others required changes in their refractive correction or other procedures. While the deficiency of tears was seldom extreme in this group, several patients showed moistening of 5 mm. or less on Schirmer's test without any corneal staining or mucoid conjunctival secretion. A few of these patients were tested repeatedly over a period of six to twelve months without showing signs of keratoconjunctivitis sicca. This suggests that additional factors may be required to produce the typical corneal and conjunctival changes. It is true, however, that the lacrimal deficiency observed was never as great as that seen in the typical Sjögren syndrome.

The patients in group II (table 1) must be considered as showing a mild form of keratoconjunctivitis sicca. The lacrimal gland appeared to be the only gland involved in most of them, although salivary deficiency may easily escape observation and was

From the Department of Ophthalmology, Northwestern University Medical School.

1. Bruce, G. M.: (*a*) Keratoconjunctivitis Sicca, Tr. Am. Ophth. Soc. **38**:149, 1940; (*b*) Keratoconjunctivitis Sicca, Arch. Ophth. **26**:945 (Dec.) 1941.

noted by a few patients. The ropy secretion seen in the typical syndrome was absent, the eyes showing either no secretion or, more commonly, a small amount of mucoid material. On gross examination the conjunctivas and corneas did not

TABLE 1.—*Group II*

No. and Name	Age	Response to Schirmer Test (Average), Mm.	Corneal Lesions	Conjunctival Lesions	Associated Changes	Treatment	Response
1. Mrs. W.	29	R 6 L 12	++	+	Dry mouth, swelling of parotid glands, slight anemia	G & L *	Not followed
2. Mrs. W.	60	R 7 L 6	Slight	Moderate	None	G & L, prostigmine hydrobromide	Improved
3. Mrs. K.	58	R 11 L 2	+, L	++, L	None	Vitamin A, G & L, closure of tear points, L	Much improved
4. Mrs. L. K. (sister of Mrs. K.)	63	R 12 L 17	Slight, R	Slight, R	None	G & L	Not followed
5. Dr. T.	51	R 3 L 21	Slight	+	None	G & L	Symptoms relieved
6. Mr. S	50	R 8 L 12	+++, R; recurrent erosion, L	+	Dry mouth	Vitamin A, G & L, closure of tear points, R	Relieved; vision improved from 20/30 to 20/15
7. E. V.	35	R 12 L 12	+; worse in L	+	None	Vitamin A, G & L	Improved slightly
8. Mrs. P.	44	R 10 L 5	Slight, R	—	None	G & L	Relieved
9. Mrs. O. K.	50	R 0 L 12	Slight, L (one examination)	—	None	G & L	Not followed
10. Mrs. C.	31	R 1 L 0	+	+	Anemia	G & L, prostigmine hydrobromide, closure of tear points advised	Not followed
11. Miss C.	67	R 4 L 6	Slight, L	Slight	None	G & L, vitamin A, ethylmorphine hydrochloride	Improved
12. J. B.	45	R 15 L 10	Slight, L	+	None	G & L, procaine hydrochloride and epinephrine hydrochloride	Improved
13. Mrs. G.	65	R 10 L 8	+	+	None	G & L	Improved
14. Mrs. R.	70	R 4 L 5	+	+	Dry mouth	G & L, vitamin A	Improved
15. Mrs. S.	75	R 7 L 5	Slight, L	Slight	Dry mouth, arthritis	G & L, vitamin A, oil at night	Slightly improved
16. Mrs. T.	53	R 6 L 4	+	++	None	G & L	Not followed
17. Mrs. F.	77	R 15 L 6	+	++	Arthritis	Vitamin A, G & L	Improved
18. Miss N.	57	R 3 L 5	++, R; +, L	++	High blood cholesterol content and sedimentation rate	G & L, closure of tear points	Improved; staphylococcic blepharoconjunctivitis developed
19. Mrs. B.	65	R 6 L 5	++	+	Dry mouth (slight), rheumatic pains, undulant fever	G & L, closure of tear points advised	Slightly improved; closure of tear points postponed
20. Mrs. F.	54	R 25 L 12	++	++	Arthritis, thyroidectomy, low basal metabolism	G & L, thyroid trouble	Improved; corneal lesions remained
21. Mr. V.	39	R 8 L 10	+; more in R	Slight	Severe asthenopia	G & L, closure of right tear points	Relieved; no staining of right cornea

* Gelatin and Locke's solution.

appear dry. A few patients even complained of "watering," a sensation probably caused by the mucoid secretion. A few of the patients had changes almost severe enough to justify classification in group III. Patient 1, for instance, had a definite history of dry mouth and swelling of the parotid glands, but the amount of tears was

greater than is typical. Patients 18 and 19 were on the borderline. In patient 20, the lacrimal deficiency was relatively slight but definite corneal changes were present in both eyes. The condition of most of the patients in this group would undoubtedly have remained undiagnosed in our practice until the Schirmer test and slit lamp examination were made routine procedures for patients complaining of ocular irritation for which no obvious cause could be found. If the slit lamp examination, after staining with fluorescein, had been used alone, we might have decided that some of the patients had the mild form of epithelial dystrophy. The differential

TABLE 2.—*Group III*

No. and Name	Age	Response to Schirmer Test (Average), Mm.	Corneal Lesions	Conjunctival Lesions	Associated Changes	Treatment	Response
1. Mrs. S.	74	R 5 L 1	++, R; +++, L	++	Dry mouth	G & L, vitamin A, closure of tear points	Much improved almost no staining of corneas
2. Mrs. F.	51	R 2 L 1	++	++	Arthritis, dry mouth	G & L, tear points had been closed	Symptoms improved
3. Mrs. G.	60	R 5 L 2	++	+	Dry mouth, arthritis	G & L, closure of tear points advised	
4. Miss W.	32	R 0 L 0	++, a few short filaments in each eye	+++	None	G & L, closure of tear points advised	Improved on temporary closure; refused permanent closure
5. Mrs. J.	72	R 7 L 28	++, R; slight, L	++, R	Arthritis	G & L, vitamin A, closure of tear points, R	Symptoms relieved
6. Dr. S.	44	R 1 L 3	++, R; +, L	+++	Arthritis, dry mouth, chronic prostatitis	G & L, closure of tear points	Relieved
7. Mrs. W.	70	R 6 L 2	+++	+++	Dry mouth, low basal metabolism	G & L, thyroid substance, closure of tear points advised	Improved, but many corneal lesions remained
8. Mrs. D.	65	R 1 L 1	++	++	Dry mouth, dietary deficiency	Vitamin A, G & L. closure of tear points	Symptoms relieved
9. Mrs. H.	63	R 0 L 0	++	++	Dry mouth, severe arthritis deformans	Vitamin A, G & L	Improved; cataract extraction, L, uneventful
10. Mrs. H.	46	R 1 L 2	++, few filaments	+++	Very dry mouth ovarian deficiency, hypothyroidism	G & L, pilocarpine nitrate, thyroid substance, estrogens, closure of tear points advised	Improved; some discomfort and some corneal lesions remained
11. B. M.	33	R 6 L 3 (after closure of tear points)	++, few filaments	++	Dry mouth, arthritis	Tear points had been closed but reopened, to be closed permanently	Relieved temporarily; condition recurred when tear points reopened
12. Mrs. S.	42	R 1 L 1	++, R; +, L	++	Dry mouth, swelling of parotid glands, arthritis	G & L, pilocarpine nitrate, closure of tear points advised	Not followed

diagnosis and possible relationships of these two conditions will be discussed later. As is seen from the tables, the lacrimal deficiency was in nearly all cases bilateral but often differed in degree between the two sides. The most severe corneal and conjunctival changes were nearly always on the side of the greatest deficiency. All but 4 patients, or 75 per cent, were women, and most were at or past the age of the climacteric, the average age being 54.2 years.

Reports of the patients with typical Sjögren syndrome, here called group III, are presented in table 2. Since the work of Sjögren,[2] well summarized by Bruce, it has been well known that this is a systemic disease involving the lacrimal and salivary glands and frequently associated with other evidences of chronic systemic infection,

2. Sjögren, H.: Acta ophth., 1933, supp. 2, p. 1; **13**:1 and 40, 1935; **16**:70 and 80, 1938.

such as arthritis, anemia, lymphocytosis and an increased sedimentation rate. As is seen in the table, all the patients except patient 4 had some of the associated changes. Seven of the 12 patients gave a history of arthritis, and in several this was of the severe, deforming variety. All but 2 complained of dry mouth, but only 1 showed swelling of the parotid glands. Swelling of other salivary glands was not observed. In nearly all the lacrimal deficiency was almost complete and bilateral, the only exception being patient 5, in whom changes in one eye were slight, while corneal changes in the other eye were pronounced and were relieved completely by closure of the tear points. All but 1 patient in this group, or 91 per cent, were women. More of the patients than in group II were in early middle age, there being patients of the ages 32, 33, 42, 44 and 46, but several much older persons brought the average age to about the same, 54.3 per cent. Some of these older patients had known of the condition for many years, and the impression seems justified that the glands are affected earlier in the typical syndrome than in the mild forms included in group II. The changes had reached extreme degrees in patient 10 at the age of 46, patient 4 at 32 and patient 6 at 44. Only 3 patients, 4, 10 and 11, showed filaments attached to the cornea. Gunderson [3] has attempted to distinguish between the filaments seen in this condition, which are short and few, from those seen in typical filamentous keratitis, which are larger and more numerous. We see no definite way to distinguish the two conditions by appearance alone.

The presence of filaments calls for a Schirmer test, and if the lacrimal deficiency proves to be severe and other causes are absent, the condition will be diagnosed as keratoconjunctivitis sicca. In our experience, filaments without lacrimal deficiency are seen only rarely and chiefly after an operation for cataract or in recurrent corneal erosion.

DIAGNOSIS

In the typical case of Sjögren's syndrome the diagnosis presents no difficulties. A dry, ropy secretion with shreds adhering to the corneal epithelium is seen in practically no other condition. Filaments may be seen, and staining with fluorescein will usually show a few areas large enough to be seen grossly. The slit lamp will show many more staining areas, of all sizes and shapes, most numerous on the lower half of the cornea. The conjunctiva appears dry, red and more or less thickened. In extreme cases it is so thick and velvety as to suggest trachoma. The associated symptoms and examination of the mouth will clinch the diagnosis. While dryness of the conjunctiva may be extreme in trachoma, scarring of the tarsus and pannus will distinguish this disease from keratoconjunctivitis sicca, in which such changes do not occur. The extensive scarring seen in ocular pemphigus will distinguish that condition. Lacrimal deficiency may be extreme in pemphigus, owing to obliteration of the secretory ducts. In 1 of our cases of pemphigus great relief from repeated corneal erosions was obtained by closing the tear points. The condition which follows removal of the lacrimal gland or obliteration of its ducts in removal of a neoplasm is in all essentials identical with keratoconjunctivitis sicca but is nearly always unilateral.

It is the mild forms, such as those included in group II, which present difficulties in diagnosis. From the symptoms and gross examination alone these forms may easily be and undoubtedly often are diagnosed as chronic conjunctivitis. Slit lamp examination after staining with fluorescein will, however, reveal corneal changes such as are seen in few other conditions.

In certain cases of superficial punctate keratitis or epidemic keratoconjunctivitis of the type described by Hogan and Crawford,[4] the corneal lesions may be super-

3. Gunderson, in discussion on Bruce.[1a]
4. Hogan, M. J., and Crawford, J. W.: Am. J. Ophth. **25**:1059, 1942.

ficial and vary enough in shape to create a certain resemblance. However a few typical circumscribed infiltrates, such as are never seen in keratoconjunctivitis sicca, are usually seen, and the history of an acute onset with lacrimation and photophobia should prevent confusion of the two conditions. As an incidental finding we did observe lacrimal deficiency in 2 cases of superficial punctate keratitis. The Schirmer test gave the following results: right 2 mm. and left 4 mm. in one case and right 15 mm. and left 4 mm. in the other. The patients lived at a distance and so have not been followed to see whether the lacrimal deficiency was a temporary condition.

As has already been stated, slit lamp examination alone might lead to a diagnosis of the mild form of epithelial dystrophy, as described by one of us. (S. R. G.).[5] It is true that more diagnoses of this condition were made in the days before routine Schirmer tests were being done. Sometimes a lacrimal deficiency was suspected and the patient was treated with a substitute for tears, but not enough effort was then made to determine whether lacrimal deficiency is a constant or important factor in the condition. Mild epithelial dystrophy was found to occur more frequently in women and in persons past middle age. Since the routine use of the Schirmer test, we have seen 2 patients with typical mild epithelial dystrophy, and in both of these the test gave results within normal limits: right eye 27 mm. and left 17 mm. in one and both eyes 30 mm. in the other. In these and the former patients

Fig. 1.—Technic of the Schirmer test.

with mild epithelial dystrophy there were no filaments and no threads of dry secretion, and, aside from the staining areas of the corneas, there was a diffuse edema of the corneal epithelium. In a few patients drusen of Descemet's membrane were present. The symptoms of dry mouth and swelling of the parotid glands were not noted in any of these patients. While it is admitted that some of the patients previously described as having mild epithelial dystrophy may have had mild keratoconjunctivitis sicca, it is believed that in others the corneal epithelium was affected without any degenerative changes in the lacrimal or salivary glands and hence that the name mild epithelial dystrophy was a proper one. There is now no doubt that a Schirmer test is indicated for every patient with lesions of the corneal epithelium to distinguish between keratoconjunctivitis sicca and mild epithelial dystrophy.

The fact that patients were seen with marked lacrimal deficiency but no corneal changes indicates that some other factor may be necessary to produce the typical picture. However, patients with complete surgical destruction of the lacrimal gland on one side always show the typical picture on the affected side.

It is seen that a diagnosis of keratoconjunctivitis sicca in its milder forms depends on a knowledge that these mild forms exist and on the routine use of a test for lacrimal function whenever the possibility of the condition exists. Bruce was not satisfied with the Schirmer test, stating that its results varied in the same patient,

5. Gifford, S. R.: Arch. Ophth. **54**:217, 1925; The Mild Form of Epithelial Dystrophy of the Cornea, ibid. **7**:18 (Jan.) 1932; Am. J. Ophth. **9**:81, 1926.

but we have found it fairly constant and, on the whole, satisfactory, provided certain conditions are observed. De Rötth [6] tried various papers and found Whatman no. 41 filter paper most dependable. It is available in most clinical laboratories and is constant in composition. Strips 35 mm. long and 5 mm. wide are cut and kept on hand. The upper 5 mm. is folded over, and we have had the upper corners cut round to avoid irritation of the conjunctiva. The folded end is laid over the lower lid at the junction of the outer third and inner two thirds (fig. 1). The patient keeps the eyes open, winking when desired. After five minutes the amount of moistened paper is measured on a millimeter rule, the upper folded portion being disregarded. It is important that no drops be used nor any manipulation performed on the lids before the test is made. Hence slit lamp examination after staining with fluorescein should be performed only after the Schirmer test. In this examination it should be remembered that the occasional contact of the filter paper with the cornea may produce delicate streaks in the epithelium which stain with fluorescein. One becomes familiar with these streaks and learns to distinguish them from lesions of keratoconjunctivitis sicca, but in case of doubt the slit lamp examination may be repeated on another day without a Schirmer test. Patients do not vary greatly on repeated tests, and a definite lacrimal deficiency found at the first test seldom fails to be confirmed.

TABLE 3.—*Neuroparalytic Keratitis*

No. and Name	Age	Side of Operation	Response to Schirmer Test, Mm.	Corneal Lesions	Treatment	Response
1. Mrs. W.	45	Left	R 30 L 13	++, L	G & L, closure of left tear points	Relieved, few staining areas left
2. Mrs. S.	46	Left	R 15 L 8	Slight, L	Alkaline buffer solution	Improved
3. Mr. K.	58	Right	R 10 L 35	Slight, L	G & L	Was having no symptoms
4. Miss M.	63	Left	R 6 L 8	One large erosion, which healed; later, slight changes, L	Alkaline buffer solution	Relieved of erosion; slight corneal changes, L

Since MacMillan and Cone [7] indicated the value of closing the tear points in the treatment of neuroparalytic keratitis, it seemed advisable to determine how frequently lacrimal deficiency exists after destruction of the gasserian ganglion. So far, only 4 patients have been available for the test. As will be seen from table 3, all showed some lacrimal deficiency on the side of operation. This was not extreme, but the difference between the eyes was clearcut in patients 1 and 3. In patient 2 there was a slight deficiency on the side operated on, while patient 4 showed moderate and practically equal deficiency on the two sides. This patient was 63 years old, and moderate lacrimal deficiency has been shown by de Rötth to be more frequent with advance in years. When, as is usually the case, the motor root of the fifth nerve is not injured, there is no anatomic reason why the operation should interfere with lacrimal secretion. Apparently it is merely the absence of normal sensory stimuli on the side of operation which causes the lacrimal deficiency, while the need for tears is probably greater under this condition. All patients were treated with a substitute for tears, and in only 1 was it necessary to close the tear points (patient 1). This gave decided relief from the external signs of irritation and

6. de Rötth, A.: Am. J. Ophth. **24**:20, 1941.

7. MacMillan, J. A., and Cone, W.: Prevention and Treatment of Keratitis Neuroparalytica by Closure of the Lacrimal Canaliculi, Arch. Ophth. **18**:352 (Sept.) 1937; **19**:278 (Feb.) 1938.

caused the areas of corneal staining to disappear almost completely. If the filter paper is placed carefully so as not to touch the cornea, it seems safe to do the Schirmer test in cases of neuroparalytic keratitis. When a definite deficiency of tears is found, closing the tear points seems to protect the cornea against the small erosions which occur frequently in this condition.

TREATMENT

The patients in group I, with lacrimal deficiency but no corneal lesions, seemed as a rule to obtain relief from symptoms of irritation by use of a substitute for tears. We have found the use of gelatin and Locke's solution, as proposed by Rucker, satisfactory, provided a preservative is added to prevent bacterial growth. Our formula for the solution is as follows:

Gelatin	0.3 Gm.
Chlorobutanol	0.3 Gm.
Locke's solution	30 cc.

Locke's solution is made as follows:

Sodium chloride	0.900 Gm.
Potassium chloride	0.024 Gm.
Calcium chloride	0.042 Gm.
Dextrose	0.100 Gm.
Sodium bicarbonate	0.020 Gm.
Distilled water	100.00 cc.

The solution is used three to six times a day or whenever symptoms of irritation are noted. It is convenient to have 4 ounces made up to be kept in the refrigerator, a half-ounce dropper bottle being filled from this and used by the patient. The smaller bottle is boiled and the dropper washed out with boiling water each time it is refilled.

Patients such as those in group II will often obtain enough relief when using this solution so that nothing further is necessary. Patients showing a more severe deficiency and more corneal lesions, however, obtain only relative relief and are much more comfortable when the tear points are closed. These were closed in 4 patients, and closure was advised for 2 others of this group. Various other therapeutic measures have been applied to patients of this group and of group III, with varying success. Attempts have been made to increase lacrimal secretion by use of parasympathomimetic agents. Pilocarpine nitrate in doses of $\frac{1}{7}$ to $\frac{1}{5}$ grain (0.008 to 0.012 Gm.) two or three times a day was tried, being given to a few patients with improvement of symptoms, especially in patient 10, group III. Prostigmine hydrobromide has been tried recently, and an attempt has been made by one of us (J. B.) to measure the effect on lacrimal secretion.

Patients with moderate lacrimal deficiency as shown by repeated Schirmer tests were given subcutaneous injections of 0.5 mg. of prostigmine hydrobromide in the clinic, and the Schirmer test was repeated after one-half to one hour. These were not the patients listed in previous tables, but most showed signs of conjunctival irritation, and a few had areas of corneal staining. No patients with the typical Sjögren syndrome with extreme lacrimal deficiency were included. Of 13 patients so treated, 11 showed a definite increase in lacrimal secretion (table 4).

The same and a few other patients were given tablets of prostigmine hydrobromide (15 mg.) to take by mouth three times a day, tests being repeated after one week. The results are shown in table 5.

As is seen from the tables, the response varied with each type of administration but was definite in a number of patients; an improvement in the response was usually accompanied by improvement in symptoms. In this group few patients

complained of the intestinal cramps sometimes noted by patients taking prostigmine, but in the treatment of other conditions (e. g. myasthenia gravis) such symptoms are often troublesome. The use of atropine sulfate for such symptoms, advised when the condition under treatment is myasthenia gravis, seems contraindicated for obvious reasons. Since most patients in groups I and II obtained relief from a substitute for tears and those with more severe manifestations from closing of the tear points, no attempt has yet been made to treat a series of patients for long periods with prostigmine, but it may be tried in the treatment of patients who refuse to have the tear points closed.

Because of the occurrence of xerophthalmia in vitamin A deficiency and a history of dietary deficiency in a few cases, as in that of patient 8, group III,

TABLE 4.—*Effect of One Injection of Prostigmine Hydrobromide* *

No.	Name	Schirmer Test Before Prostigmine (Average)		Schirmer Test After Prostigmine (Average)	
		Right, Mm.	Left, Mm.	Right, Mm.	Left, Mm.
1	M. T.	3	6	21	26
2	M. M.	10	12.5	15	16
3	M. E.	13	30	30+	30+
4	G. K.	9	20.5	12.5	16
5	J. B.	2	7	6	24
6	W. O.	3.5	3.5	9	7
7	E. G.	22.5	8.5	25	19.5
8	J. M.	23.3	18.6	30+	26
9	A. C.	10	15	15.5	24
10	L. G.	14.5	27.5	21.5	30+
11	M. H.	9.3	19.6	15	30+
12	L. H.	0	6	15	30+
13	V. G.	3	5	16	20

* Supplied by Hoffmann-La Roche, Inc.

TABLE 5.—*Effect of Oral Use of Prostigmine Hydrobromide*

No.	Name	Schirmer Test Before Prostigmine (Average)		Schirmer Test After Prostigmine (Average)	
		Right, Mm.	Left, Mm.	Right, Mm.	Left, Mm.
1	V. G.	3.5	5	22	30
2	A. C.	10	15	10	12
3	J. B.	3	7	4	23
4	Mrs. N.	7	5	30	22
5	Mr. K.	10	10	30	26
	Average	7	8	19	23

adequate amounts of vitamin A were added to the diet of a number of the patients. Since this supplementary treatment was usually begun along with other treatment, it was difficult to judge its effect. Blood was drawn from a few patients in groups II and III and tested directly for vitamin A by one of us (I. P.). In none was a deficiency found. It seems that a vitamin deficiency is rarely a factor in the condition, but it is probably best to be sure that the patient is receiving an adequate diet or, if there is doubt, is receiving a supplement in concentrated form.

Other forms of systemic treatment thought to be of value occasionally were the use of thyroid extract when the metabolism was low (patients 7 and 10, group III and patient 20, group II) and of estrogenic extract (patient 10, group III).

In the patients of group III only relative relief of symptoms was afforded by a substitute for tears and other palliative methods. Closure of the tear points, however, always produced a decided improvement in vision when this had been

reduced by corneal lesions. Some staining areas persisted in a number of patients, and there was some persistent conjunctival secretion, but this was much reduced. Most patients preferred to continue using the mixture of gelatin and Locke's solution, but some discontinued its use and remained fairly comfortable. It was surprising to observe the changes resulting from the retention in the sac of the small amount of lacrimal secretion existing, an amount so small in some patients as hardly to be detected by the Schirmer test.

It was at first thought that closure of the tear points could be satisfactorily performed by application of pure trichloroacetic acid to the dilated canaliculus, and this opinion was expressed by one of us in discussing Bruce's paper. It was found, however, that the relief obtained with this method of closure, while lasting for several weeks, was almost never permanent. Various methods were tried, including Verhoeff's suggested method of dissecting the canaliculus out around a probe.

Fig. 2.—Method of closing canaliculus.

This was done in patient 5, group III with an excellent result, but proved to be a somewhat time-consuming procedure.

In recent cases the following procedure has been employed, with a satisfactory and usually permanent result (fig. 2): The tear point is dilated after injection of procaine hydrochloride solution along its course, and a no. 2 Bowman probe is passed as far as the common canaliculus. Two sutures are placed around the canaliculus, the probe acting as a guide. One is placed 6 mm. from the tear point and the other just beneath it. A corneal applicator with a tapering point finer than a tear point dilator is heated in a flame to red heat, and as the probe is removed the applicator is inserted to a point past the second suture, or about 7 mm. from the tear point. As it is removed the sutures are tied tightly. The procedure is repeated on the upper canaliculus. The sutures are removed in six days, at which time the lumens of the canaliculi have become completely obliterated.

In no case has epiphora developed after closure of the tear points, but this has seldom been employed unless repeated Schirmer tests have shown less than 5 mm. of wetting.

In 3 cases, recanalization of the canaliculus occurred from several months to a year after the procedure and it was necessary to dissect out one or both canaliculi. This may be done with little sacrifice of skin or conjunctiva and with little change in the inner angle. The skin and conjunctiva are sutured carefully together after the canaliculus is removed. The result of this procedure is, of course, permanent.

SUMMARY

Keratoconjunctivitis sicca, especially in its milder form, is a fairly common cause of persistent ocular irritation.

Use of the Schirmer test and slit lamp examination when there are symptoms of chronic irritation will reveal this condition.

When the condition is mild, use of gelatin and Locke's solution as a substitute for tears gives much relief of symptoms.

When it is severe, closure of the tear points is indicated.

Methods of permanent closure are described.

720 North Michigan Avenue.

PRIMARY HERPES SIMPLEX KERATITIS

CLINICAL AND EXPERIMENTAL STUDY

CAPTAIN EDWARD GALLARDO
MEDICAL CORPS, ARMY OF THE UNITED STATES

The widespread occurrence of herpetic infections, both latent and active, is well recognized; it is estimated that 80 to 90 per cent of the adult population have had herpes and are carriers of the virus in a dormant state in the epithelium of the mouth, conjunctiva or sexual organs, and perhaps also in nerve tissue. Recurrent attacks of the disease may be precipitated by a wide range of conditions, such as exposure to sun or wind, fever, menstruation and trauma. Ocular herpetic infection is clearly endogenous in the majority of cases, but that it may occasionally be exogenous has been suggested by the theory of droplet contamination by the saliva of human carriers of the virus. Contaminated utensils, clothing, etc., may provide indirect sources of spread. These and other epidemiologic factors, not concerned in this paper, are discussed in the work of van Rooyen and Rhodes.[1]

The findings of Dodd and associates[2] and of Burnet and Lush[3] on aphthous stomatitis in infants and young children add considerable evidence in support of the belief that the primary nature of a herpetic lesion can be established by the absence of herpetic antibodies in the blood at the onset of symptoms and by their presence during convalescence.

The literature available on herpes keratitis shows that the virus causation can be confirmed by passage of scrapings from the human lesion onto the scarified cornea of the rabbit.[4] To my knowledge there are no reports suggesting the possibility of primary infections in the eyes of children or adults. It is interesting, therefore, to consider the results of serum antibody titration experiments carried out in a group of 5 cases of herpes keratitis in which the history revealed no trace of previous herpetic infection in any location. The ocular symptoms in all these cases were usually severe.

EXPERIMENTAL STUDIES

In each of the 5 cases the following procedure was carried out: anesthesia was induced with 0.5 per cent pontocaine hydrochloride, and then epithelium was scraped from the affected cornea with a sterile pear-shaped platinum spatula (0.25 mm. thick and 8 by 10 mm. in area). The scrapings were diluted into 0.2 cc. of physiologic solution of sodium chloride in Wassermann tubes and amounts of 0.05 cc. immediately inoculated intracerebrally into mice, the residues being scarified into 2 rabbits' corneas; owing to the small amounts of material obtainable from the

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From the Department of Ophthalmology, Columbia University College of Physicians and Surgeons, and the Institute of Ophthalmology, Presbyterian Hospital.

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1. van Rooyen, C. E., and Rhodes, A. J.: Virus Diseases of Man, London, Oxford University Press, 1940, pp. 148-151.

2. Dodd, K.; Johnston, L. M., and Buddingh, G. J.: J. Pediat. **12**:95, 1938.

3. Burnet, F. M., and Lush, D.: Lancet **1**:629, 1939.

4. Löwenstein, A.: Klin. Monatsbl. f. Augenh. **64**:15, 1920. Grüter, M.: ibid. **65**:398, 1920. Grandstrom, K. O.: Acta ophth. **15**:361, 1937. Gundersen, T.: Herpes Corneal, with Special Reference to Its Treatment with Strong Solution of Iodine, Arch. Ophth. **15**: 225 (Feb.) 1936.

patients, no attempts were made to inoculate chorioallantoic egg membranes directly. The mice showed typical symptoms of herpetic encephalitis, as described by Andervont,[5] and died within four to five days, while the rabbits showed typical keratoconjunctivitis at the end of thirty-six to fifty hours. Herpes virus was recovered in all cases from these animals and its identity confirmed by further passage in mice and rabbits or by the production of typical herpes foci on the chorioallantois with dilutions up to 10^{-3} (table 1).

For the purpose of serum titrations, blood was taken from 4 patients during the first three days of symptoms and from 1 patient on the sixth day. Blood was taken again sixteen to eighteen days later except in the last case. The virus used in these tests was isolated from the fluid of a herpes blister of the lip and then passed through several generations of mice intracerebrally and through egg membranes; it was stored at 4 C. without a preservative, before grinding. In each titration an immune and a nonimmune serum were included as controls.

TABLE 1.—*Recovery of the Virus*

Case Number	Corneal Scrapings Inoculated Onto: Rabbit Cornea, 1 Drop, Scarified	Corneal Scrapings Inoculated Onto: Mouse Brain, 0.03 Cc., Inoculum	Mouse Brain Inoculated Onto Eggs, 0.1 Cc., Inoculum	Rabbit Scrapings Inoculated Onto Eggs, 0.2 Cc., Inoculum
1	2* / 2	4 / 4	5 / 6	6 / 6
2	2 / 2	3 / 4	4 / 6	4 / 5
3	1 / 2	4 / 4	6 / 6	5 / 6
4	2 / 2	3 / 4	5 / 6	5 / 6
5	2 / 2	4 / 4	6 / 6	4 / 6

* The upper numerals represent the number of positive reactions and the lower numerals the number of animals inoculated.

In the preliminary experiments, bacterially sterile saline suspensions of 10^{-2} and 10^{-3} dilution of the mouse brain virus, in doses of 0.03 to 0.05 cc. administered intracerebrally, killed mice at the end of three days. Inoculations of 0.1 cc. of the same dilutions transferred onto membranes of eggs incubated twelve to fourteen days produced countable foci in the majority of instances. According to the procedure of Shaffer and Enders,[6] mixtures of equal volumes of virus and individual serums were set up to final virus dilutions of 10^{-2} and 10^{-3}; these were plated on blood agar, to rule out contamination, and stored one hour at 4 C. At the end of this period each of the virus-serum mixtures was inoculated into six eggs (three for each dilution) in accordance with the technic of Burnet[7] except that the shell cuts were sealed with paraffin-soaked lens paper instead of with a cover glass.

On the basis of the immunologic evidence discussed at the beginning of this paper, and accepted so far as a criterion, the failure of 5 of the patients' serums to

5. Andervont, H. B.: J. Infect. Dis. **44**:383, 1929.

6. Shaffer, M. F., and Enders, J. F.: J. Immunol. **37**:383, 1939.

7. Burnet, F. M.: The Use of the Developing Egg in Virus Research, Medical Research Council, Special Report Series, no. 220, London, His Majesty's Stationery Office, 1936.

neutralize the herpes virus on eggs at the onset of symptoms, coupled with the nearly complete neutralization with 4 of the serums taken sixteen to eighteen days later, indicates the possibility that in these cases there was primary infection of the cornea (table 2).

It should be mentioned here that in an additional 17 cases of herpes keratitis in adults, studied in the department of Ophthalmology of Columbia University College of Physicians and Surgeons, by membrane titration methods, the patients' serums possessed marked neutralization power against herpes virus at the time of admission.

TABLE 2.—*Serum Titrations on Egg Chorioallantoic Membranes*

Case Number (Serum)	Virus Dilutions	2-3 Days of Symptoms; No. of Foci/Membrane; 0.1 Cc. of Inoculum	16-18 Days of Symptoms; No. of Foci/Membrane; 0.1 Cc. of Inoculum
1	10^{-2}	C* 50— D†	20 0 0
	10^{-3}	30 15 20	0 16 0
2	10^{-2}	50— C C	0 0 0
	10^{-3}	40 22 10	0 0 0
3	10^{-2}	C C 90—	3 0 8
	10^{-3}	D 25 20	0 2 0
4	10^{-2}	20 38 15	0 0 12
	10^{-3}	10 10 13	0 0 0
		6th day of symptoms	
5	10^{-2}	37 25 36	No blood taken
	10^{-3}	50 D 18	
Five immune serums	10^{-2}	Average number of foci on 28 eggs, 8	
	10^{-3}	Average number of foci on 30 eggs, 2	
Three nonimmune serums	10^{-2}	Average number of foci on 23 eggs, 70	
	10^{-3}	Average number of foci on 25 eggs, 21.6	

* C indicates a confluent lesion.
† D indicates death.

TABLE 3.—*Herpes Virus Infection in Rabbits' Eyes*

No. of Rabbits	Method of Inoculation	Keratoconjunctivitis Developed in: Inoculated Eyes	Keratoconjunctivitis Developed in: Control Eyes	Virus Recovered from Ocular Lesions and Transferred Onto: Rabbit Cornea	Mouse Brain	Eggs
12	Virus dropped	12*	0	4	20	6
		12		4	24	8
14	Virus swabbed	14	0	4	23	8
		14		4	28	8
10	Virus scarified	10	0	4	17	7
		10		4	20	8

* The upper numerals represent the number of positive reactions and the lower numerals the number of animals inoculated.

The history in every case in this group showed one or more cutaneous herpetic attacks previous to the ocular involvement.

In the course of a series of rabbit inoculations it was found that an infection of the cornea could be produced with little or no scarification of the epithelium. To verify this finding one eye of each of a group of 12 albino rabbits was inoculated with 1 drop of a 1:10 saline suspension of freshly ground mouse brain virus, which was deposited without scarification or rubbing in the lower conjunctiva. In another group, the conjunctiva of one eye of each of 14 rabbits was gently swabbed with undiluted secretion from the eyes of rabbits with herpetic lesions three to four days old. Ten eyes of a third group of rabbits were inoculated with mouse brain virus by the ordinary method of corneal scarification. The fellow eye of each animal was kept as a normal control. Typical herpetic keratoconjunctivitis, varying some-

what in severity, developed in all inoculated eyes of the three groups within three to four days, the secretions remaining scanty, nonpurulent and free of gross bacterial contamination throughout this period. The corneal lesions in the nonscarified eyes developed from twelve to eighteen hours later than such lesions in the scarified eyes. Otherwise they were similar in behavior, duration and sequelae. Herpes virus was subsequently recovered from all inoculated eyes of the three groups by intracerebral inoculations in mice. It was also recovered from 4 eyes chosen at random from each group by means of chorioallantoic inoculations and by further passages through rabbits' corneas (table 3).

These results show that, given the proper concentration of virus and a susceptible host, herpetic infections of the cornea and conjunctiva can be produced without mechanical trauma of the corneal or conjunctival epithelium; a fact which, as far as I know, has not previously been reported.

SUMMARY AND CONCLUSIONS

1. Herpes-neutralizing antibodies were not found two to three days after the onset of symptoms in 4 of 5 cases of dendritic keratitis without a history of previous corneal or cutaneous herpetic infection. In the fifth case there were no antibodies on the sixth day of symptoms. Blood taken in 4 of the cases sixteen to eighteen days later showed a definite neutralizing power against herpes virus. It is believed that these cases represent primary exogenous herpetic lesions. In 17 other cases of dendritic keratitis with a history of previous corneal or cutaneous herpes, there were neutralizing antibodies at the onset of the keratitis, and these cases are believed to represent secondary endogenous herpetic infections.

2. Typical herpetic keratoconjunctivitis was produced in rabbits by dropping or swabbing virus material into their conjunctival sacs; the feasibility of transmission of herpes virus infection without mechanical disturbance of the epithelial lining was thus established.

Dr. Phillips Thygeson's cooperation made this work possible.

638 West One Hundred and Sixty-Eighth Street.

THERAPEUTIC EXPERIENCES WITH CORNEAL ULCER DUE TO BACILLUS PYOCYANEUS

EARL H. BROWN, M.D.
TUCSON, ARIZ.

For years, in going over the literature on corneal ulcer, I have noticed that all standard textbooks agree on one point—that corneal ulcer is a malignant disease and when due to Bacillus pyocyaneus usually leads to loss of the eye or at least to loss of sight. These facts made little impression on me until the summer of 1942, when I encountered 3 cases of B. pyocyaneus corneal ulcer, and the experience with these cases is herein reported. It may seem illogical to draw any conclusion from 3 cases; however, such ulcer is extremely rare. Joy,[1] reporting in June 1942, said that only 64 cases had been reported in the literature, 23 of them having been reported since 1922. A tabulation showed loss of the eyeball in 12, total loss of sight in 3, loss of sight to 1/10 in 4 and reduction of vision in 4.

Joy gave a complete review of the literature and stated that to date therapy had been unsuccessful in halting the course of the disease. He produced B. pyocyaneus ulcer in rabbits' eyes and studied the effect of oral administration of sulfapyridine (2-[paraaminobenzenesulfonamido]-pyridine). In 87 per cent of the animals which received the drug within six hours after inoculation, the ulcer healed by the sixth day. Of the animals which began to receive the drug eighteen hours after inoculation, 80 per cent showed a favorable effect and in 57 per cent the ulcer had healed by the end of the seventh day. Given prophylactically, by mouth, sulfapyridine was apparently effective in modifying the course of the disease. Joy did not report on any case of use of the drug in the treatment of a human eye.

Most authors agree that the sulfonamide compounds permeate effectively the ocular tissues in the order named—sulfapyridine, sulfanilamide, sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine) and sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole).

Liebman and Newman[2] studied the concentration of the sulfonamide compounds in the aqueous humor as compared with the blood in rabbits. They found that the levels of sulfapyridine and sulfanilamide were two thirds as high in the aqueous as in the blood. The level of sulfadiazine was one half as great in the aqueous as in the blood and the level of sulfathiazole one fifth as great.

Scheie and Leopold[3] got approximately the same figures in their experiments and found that they could raise the level of the drugs in the aqueous by giving vasodilator drugs.

Chinn and Bellows[4] studied the concentration of the sulfonamide compounds in the aqueous after local application. They found that sulfanilamide most readily

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From the Thomas-Davis Clinic.

1. Joy, H. H.: Treatment of Experimental Bacillus Pyocyaneus Ulcer of Cornea with Sulfapyridine, Arch. Ophth. **27**:1135-1164 (June) 1942.

2. Liebman, S. D., and Newman, E. H.: Distribution of Sulfanilamide and Its Derivatives Between Blood and Aqueous, Arch. Ophth. **26**:472-477 (Sept.) 1941.

3. Scheie, H. G., and Leopold, I. H.: Penetration of Sulfathiazole into the Eye, Arch. Ophth. **27**:997-1004 (May) 1942.

4. Chinn, H., and Bellows, J. G.: Corneal Penetration of Sulfanilamide and Some of Its Derivatives, Arch. Ophth. **27**:34-39 (June) 1942.

penetrates the cornea. The powdered form, they stated, is preferable to the ointment. They suggested that oral medication is the most reliable.

Osgood [5] recommended local application of a 10 to 20 per cent suspension of powdered sulfathiazole in one of the water-soluble lubricating jellies or use of a constant drip of saturated solution of sulfathiazole in 0.85 per cent saline solution (1.5 Gm. per liter).

Lepard [6] reported 3 cases of B. pyocyaneus ulcer, in 2 of which the eye was enucleated. The eye in the third case, in which sulfapyridine therapy was employed, was saved (20/30 vision).

The 3 cases reported here parallel this experience. The sulfonamide compounds did not seem to be of much value locally. Sulfapyridine given by mouth seemed to be beneficial.

Treatment consisted of practically all the routine procedures, including the following ones: instillation of atropine sulfate solution; use of hot packs; irrigations; application of antiseptic ointments, such as mercury bichloride and sulfathiazole ointment; cauterization with trichloroacetic acid; application of tincture of iodine; use of the actual cautery; oral administration of sulfadiazine and sulfapyridine; protein shock, such as that produced by injections of milk; infrared light therapy, and, finally, incision into the anterior chamber by the Saemisch method.

After observation of these cases, the following conclusions were reached:

1. When B. pyocyaneus is observed in culture of material from an ulceration in the eye, the prognosis is extremely grave in spite of all treatment.

2. Of all the local therapy, early use of the actual cautery or diathermy needle is the best; chemical cauterization did not seem sufficient.

3. Use of atropine sulfate solution and the usual hot packs and irrigations are, of course, indicated.

4. When the ulcer continues to progress and infiltrate into the cornea, the Saemisch maneuver is indicated.

5. Sulfapyridine or sulfanilamide administered by mouth is the drug of choice.

6. The sulfonamide compounds applied locally did not show any advantage over the usual antiseptics, such as mercury bichloride ointment.

REPORT OF CASES

CASE 1.—H. E. M., a man aged 47, a railroad yardman, came to the office on June 18, 1942. A deeply embedded foreign body was removed from the left upper quadrant of the right cornea, pontocaine hydrochloride anesthesia being used. He returned June 19, 1942 with a moderate reaction in the eye and a small ulcerated area around the wound. The eye was dilated with atropine sulfate solution and merthiolate in a 1:5,000 dilution instilled. The patient returned June 20, with a large ulcer complicated by iritis. At this time the ulcer covered one fourth of the cornea. It was cauterized with trichloroacetic acid, and he was admitted to the hospital.

Treatment consisted of oral administration of sulfadiazine, application of sulfathiazole ointment in the eye, use of hot packs and of atropine sulfate and intramuscular injections of milk.

By June 21 the ulcer had covered the entire front of the cornea in spite of all treatment. The anterior chamber was cloudy, and the entire eye was inflamed.

June 24 the ulcer was seen to be progressively destructive and the cornea began to slough. Consultation was held with Dr. T. H. Cates, and a paracentesis through the ulcer was performed.

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5. Osgood, E. E.: Principles Which Should Govern the Local Use of the Sulfanilamide Drugs, Surg., Gynec. & Obst. **75**:21-27 (July) 1942.

6. Lepard, C. W.: Bacillus Pyocyaneus Ulcer: Report of Three Cases; Results of Sulfapyridine Therapy in One Case, Tr. Am. Acad. Ophth. **46**:55-60 (Nov.-Dec.) 1941.

June 25 the condition of the eye was unimproved and the patient was referred to the Southern Pacific General Hospital, in San Francisco, where the eye was enucleated July 2.

The laboratory report on June 25 was as follows: "A direct smear shows neither pus cells nor organisms. Cultures in beef heart infusion broth and blood agar show large gram-negative, actively motile bacilli. Subcultures made on dextrose, sucrose, maltose, lactose, xylose, mannitol and iron agar show neither acid nor gas. Culturally the organism belongs to the Alcaligenes group (B. pyocyaneus)."

CASE 2.—B. F., a man aged 27, a railroad brakeman, had a deeply embedded metal foreign body removed from the left outer surface of the left cornea on July 10, 1942. Pontocaine hydrochloride anesthesia was employed. Metaphen solution, 1:5,000, and atropine sulfate solution were instilled and a bandage applied.

July 11 the conjunctiva was slightly injected, but the cornea looked clean. The same treatment was carried out.

July 12 the patient called during the night, saying that he had severe pain in the eye. When he was seen in the office the conjunctiva was severely inflamed. There was some ulceration around the wound. This was cauterized with trichloroacetic acid, and the patient was referred to the hospital. Treatment consisted of administration of sulfathiazole by mouth, injections of milk, use of sulfathiazole ointment and, once a day, instillation of optochin hydrochloride solution.

By July 13 the ulceration had spread, and after consultation with Dr. T. H. Cates a Saemisch operation was performed. Thereafter the patient improved symptomatically, but the entire eye was now inflamed and the anterior chamber cloudy.

July 14 the anterior chamber was draining freely through the incision. The eye was less painful.

July 15 the entire eye was acutely inflamed, with some edema of the lids. The wound was still draining. The pupil was dilated with 10 per cent emulsion of neo-synephrin hydrochloride and atropine sulfate to prevent prolapse of the iris into the wound.

July 16 the patient was referred to the Southern Pacific General Hospital, in San Francisco, where the eye was treated for ten days and finally enucleated.

A laboratory report, made July 21, was as follows: "A broth culture of material swabbed from the eye shows many gram-negative motile bacilli and a few staphylococci. Cultures in broth, on blood agar and on chocolate agar show gram-negative bacilli to be the predominating organisms. Rare gram-positive cocci and gram-positive bacilli are also present. Subcultures in broth and on desoxycholate agar show pure culture of gram-negative, non-lactose-fermenting, actively motile bacilli in large mucoid colonies. Subcultures on sucrose, lactose, maltose, dextrose, xylose, mannitol and Russell's double sugar agar show neither acid nor gas after twenty-four hours."

Cultures disclosed no change after six days. Gelatin was liquefied by the organisms. Potato showed a slightly blue-green color. Culturally the organism appeared to be B. pyocyaneus.

CASE 3.—E. B. K., a man aged 35, a railroad brakeman, had a foreign body removed from the center of the right cornea July 16, 1942. He came to the office July 17. Some stained corneal tissue was curetted from the wound, and atropine sulfate solution and mercury bichloride ointment (1:5,000) were instilled.

July 18 there was a small amount of slough in the wound. Metaphen solution, 1:5,000, and mercury bichloride ointment were instilled.

July 19 the wound appeared ulcerated and the conjunctiva was injected. The ulcer was cauterized with trichloroacetic acid and the patient referred to the hospital. Treatment consisted of administration of 15 grains (1 Gm.) of sulfapyridine every four hours, use of hot packs, instillation of atropine sulfate solution and of mercury bichloride ointment and intramuscular injections of milk.

July 20 the ulceration was spreading. With local pontocaine hydrochloride anesthesia, the entire ulcerating area was thoroughly cauterized with a diathermy needle. The other treatment was continued.

July 21 the eye was less painful and otherwise somewhat improved. The area of ulceration had not increased. The level of sulfapyridine in the blood was 5 mg. per hundred cubic centimeters. The eye continued to improve with the same treatment, and the patient was able to leave the hospital July 27. He returned to the office for daily treatments with short wave diathermy, and the use of sulfapyridine was discontinued.

August 3 the ulcer was healing around the periphery, and a central soft area was again cauterized with the diathermy needle. Instillation of atropine sulfate solution, irrigation with boric acid and use of mercury bichloride ointment were carried out during the next month, and the area was entirely healed by September 15. The patient had a large scar over the entire anterior surface of the cornea except for a clear area above. Vision was 10/400.

The eye was entirely free of inflammation, and the anterior chamber and vitreous were clear. With the pupil dilated the eyeground could be seen around the scar, and it was normal. A peripheral iridectomy above and to the outer quadrant of the iris later should give good, useful vision.

A laboratory report on July 27 was as follows: "Broth culture shows staphylococci and actively motile gram-negative bacilli. Subcultures on blood agar and desoxycholate agar show many large mucoid colonies of gram-negative, non-lactose-fermenting bacilli and a few colonies of staphylococci. Subcultures on dextrose, maltose, xylose, mannitol and Russell's double sugar agar show neither acid nor gas after twenty-four hours."

There was no change after six days. Gelatin was liquefied. A peptone solution culture did not show indol.

Growth on potato showed a faint blue-green color after forty-eight hours. Culturally the organism appeared to be B. pyocyaneus.

ACHROMATOPSIA

REPORT OF THREE CASES

SAMUEL D. LEWIS, M.D.
HARTFORD, CONN.
AND
JOSEPH MANDELBAUM, M.D.*
BROOKLYN

Achromatopsia, or complete color blindness, is a relatively rare anomaly which is usually associated with profound visual disturbances. When this is the case, all the symptoms accompanying the lack of color perception are attributable to complete absence of photopic vision. Since it is the cone mechanism of the retina which mediates photopic vision, it can be concluded either that the cone cells are absent or, if present, are not functioning. Histologic evidence points to the second of these possibilities [1]; however, little anatomic material has been available.

The typical symptoms accompanying achromatopsia include a marked reduction in visual acuity, central scotoma, ocular nystagmus, photophobia and a shift of the spectral visibility curve. Instead of maximum brightness occurring in the yellow region of the spectrum (555 millimicrons), which is the normal photopic peak, it occurs in the green region (510 millimicrons), which is the peak for normal eyes only when low scotopic levels of illumination are employed. Because of the shift of the curve toward the shorter wavelengths, visibility at the red end of the spectrum is greatly diminished.

These changes are easily explained if it is assumed that the cone cells are not functioning. The central scotoma and ocular nystagmus are due to a non-functioning fovea. The highest degree of visual acuity that the rods are capable of is approximately 20/200. The fact that even under high photopic levels of illumination the brightest spectral region remains at the normal scotopic peak (510 millimicrons) confirms the belief that only the rod mechanism is functioning. Finally, since rod cells function most efficiently at very low illuminations, ordinary photopic levels of illumination are uncomfortable and give rise to photophobia.

Occasionally a completely color blind person retains the other characteristics of normal photopic vision and has good visual acuity, a normal photopic visibility curve and no central scotoma or ocular nystagmus. Such persons have been referred to as having atypical achromatopsia.[2] In her series of 119 completely color blind subjects, Bell [3] found only 4 who retained the other features of photopic vision. It cannot be assumed that in atypical achromatopsia the cone cells are not functioning, because normal visual acuity and the normal photopic visibility curve would be impossible with a cone-free retina. The atypical form can readily be

*Fellow in Ophthalmology, Long Island College of Medicine.

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3. Bell, J.: Color Blindness, Treasury of Human Inheritance, University of London, Francis Galton Laboratory for National Eugenics, Eugenics Laboratory Memoir 23, 1926, vol. 2, pt. 2.

classified in terms of the Thomas Young trireceptor theory of color vision. Normal color vision, in which there are presumably three color receptors functioning, is termed trichromatism. The most modern concept, in line with other aspects of the photochemical nature of the photosensory process, is that the three receptors are three different cone cells containing photosensitive pigments with slightly different spectral sensitivities.[4] It is the differential effect of chromatic stimuli on these three receptors which permits the retina to distinguish colors. In the most common type of color blindness only two different color receptors are functioning. This condition is called dichromatism and is referred to as protanopic, deuteranopic or tritanopic, according to whether the hypothetic red, green or violet receptor is missing. When only one photopic receptor is functioning, the condition may be called monochromatism. The general characteristics of photopic vision will be retained, such as normal visual acuity and a visibility curve with maximum spectral brightness in the yellow (555 millimicrons). However, there will be complete color blindness, since there can be no differential effect if there is only one receptor. Hence all colors of the spectrum will appear colorless and may be matched with white light. Bell's 4 patients and other subjects listed as having atypical achromatopsia may well be designated as monochromatic, in contrast to the typical, purely scotopic subjects, who may best be designated as achromatic.

It is somewhat more difficult to explain the remnant of color vision, usually for a color at an end of the spectrum, which is occasionally preserved in otherwise monochromatic subjects.[2] Several possible explanations may be given, however. A small number of elements of a second receptor may be functioning, giving an anomalous dichromatic condition, analogous to anomalous trichromatism, which is commonly seen. Another possible explanation is that the brightness sensation elicited by the cone cells may differ qualitatively from the brightness sensation given by the rod cells. At certain levels of illumination, both the cone cells and the rod cells will be functioning,[5] the rod function present being greatest at the violet end of the spectrum and disappearing entirely at the red end, where the rod cells are insensitive to light and there is no photochromatic interval.[6] Chromatic stimuli will appear as an admixture of the two (rod and cone) sensations for violet light, but as the pure cone sensation for red light, allowing a basis for some crude color differentiation. Both of these explanations are concerned with the retina. Another possibility exists: The retina may be completely normal, with the three photopic color receptors intact, the defect existing cerebrally in the color fusion center. This explanation is valid only for monochromatism and not for achromatism, in which the defect is certainly retinal.

REPORTS OF CASES

We had the opportunity to study 3 siblings of French Canadian parentage who manifested all the typical features of achromatopsia. In addition to the usual ophthalmologic examination, dark adaptation tests were made on all 3 subjects, and the spectral visibility of 2 of the subjects was determined.

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6. Hecht, S.: Rods, Cones, and the Chemical Basis of Vision, Physiol. Rev. **17**:239, 1937.

CASE 1.—E. O., a girl of 15, first visited one of us (S. L.) on Jan. 7, 1941, complaining of poor vision, photophobia and color blindness. These symptoms had been present all her life. The medical history was essentially irrelevant. Examination revealed a fairly well built girl completely normal for her age and showing no gross evidence of congenital anomalies in her physical makeup.

The visual acuity was 20/300 in the right eye and 20/300 in the left. The lids and conjunctivas were normal. The corneas were clear on slit lamp examination and exhibited normal sensitivity. The pupils were round and equal and reacted rather sluggishly to light and in accommodation. The media were clear. The retinal fundi showed no abnormalities, the optic disks, macular regions and retinal blood vessels being completely normal. There were no hemorrhages, exudates or other evidence of degenerative lesions. A coarse horizontal pendular nystagmus was present in all directions of gaze. An alternating concomitant exotropia of about 20 degrees was present. Retinoscopy with homatropine cycloplegia revealed the presence of compound hyperopic astigmatism; right eye, + 3.00 D. sph. ⌒ + 1.50 D. cyl., axis 90, and left eye,+ 1.50 D. sph. ⌒ + 3.00 D. cyl., axis 90. However, neither lenses nor a pinhole could improve the visual acuity. Peripheral fields determined with a 1 degree white test object under 7 foot candles of illumination were within normal range. With the use of a 2 mm. white test object on the tangent screen at 1 meter central scotomas measuring about 1 degree in radius could be demonstrated. Color discrimination seemed to be entirely lacking, all colors appearing simply as shades of gray.

CASE 2.—C. O., a man of 22 employed as a plumber's helper, was first seen by one of us (S. L.) on March 25, 1942. His complaints were poor vision, photophobia and color blindness. He had had these symptoms all his life. His medical history included five episodes of pneumonia, and mastoiditis on the right side, treated surgically, in 1930. Physical examination revealed a well developed young man free from any gross evidence of congenital anomaly.

The visual acuity was 20/200 in the right eye and 20/200 in the left. The lid margins of both eyes were hyperemic and scaly; there were no ulcerations. The conjunctivas were normal. The corneas were clear and had normal sensitivity. The pupils were round, the right one being slightly larger than the left, and reacted rather sluggishly to light and in accommodation. The ocular media were clear. The optic disks, macular regions and retinal blood vessels were normal. There were no hemorrhages, exudates or other evidence of a degenerative retinal lesion. A coarse horizontal nystagmus was present in all directions of gaze. A left concomitant exotropia of 30 degrees was present. Retinoscopy with hematropine cycloplegia revealed compound myopic astigmatism: right eye, —1.00 D. sph. ⌒ —2.75 D. cyl., axis 180, and left eye, —0.75 D. sph. ⌒ —3.50 D. cyl., axis 180. No improvement in visual acuity could be obtained either with lenses or with a pinhole. Peripheral visual fields as measured with a 1 degree white object under 7 foot candles of illumination were normal. Examination with the tangent screen, a 2 mm. white test object at 1 meter being used, demonstrated the presence of central scotomas of 1 degree radius. Color discrimination seemed to be entirely lacking; all colors were described as shades of gray.

CASE 3.—A. O. G., a 27 year old housewife and the mother of two children, was first seen by one of us (S. L.) on April 25, 1942. Her complaints were those described by her brother and her sister. Her medical history was essentially unimportant. Examination revealed a rather obese young woman with no gross evidence of congenital anomaly.

The visual acuity was 20/200 in the right and 20/200 in the left eye. The lids and conjunctivas were normal. The corneas were clear on slit lamp examination, and showed normal sensitivity. The pupils were round and equal and reacted to light and in accommodation. The ocular media were clear. The optic disks, macular regions, retinal blood vessels and retinal background appeared entirely normal. A pendular horizontal nystagmus was present in all directions of gaze. A left exotropia of 45 degrees was present, as well as a left hypertropia, which could not be accurately measured. Retinoscopy with homatropine cycloplegia revealed compound hyperopic astigmatism in the right eye: + 2.00 D. sph. ⌒ + 1.50 D. cyl., axis 90. In the left eye there was mixed astigmatism: — 50 D. sph. ⌒ + 2.25 D. cyl., axis 90. No improvement in visual acuity could be obtained with either lenses or a pinhole. The peripheral and central visual fields were studied as in the other cases. The peripheral fields were found to be normal, but central scotomas measuring about 2½ degrees in radius were demonstrable. Color vision seemed to be entirely lacking; all colors were referred to as gray.

The family history of achromatopsia is best described by the genetic tree given in figure 1. The maternal ancestry is shown in detail. There were no known cases

of achromatopsia in the paternal tree. The black circles indicate persons with color blindness and poor vision. The hereditary pattern seems to be that of a simple recessive characteristic, without sex linkage. In this respect it is consistent with the pattern described in the majority of cases of achromatopsia.[3] The subjects described in this paper are the 3 affected siblings in the fourth generation. Of interest is the consanguinity indicated on the chart; the father's and mother's grandparents were siblings. Achromatopsia appears in two cousins of our subjects, however, without any evidence of consanguinity.

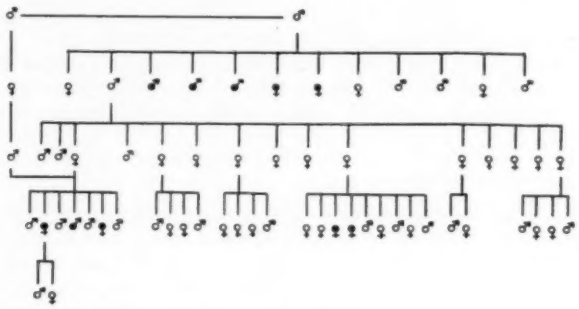

Fig. 1.—Inheritance of achromatopsia. Our subjects are the 3 affected siblings in the fourth generation; these are the only ones actually studied.

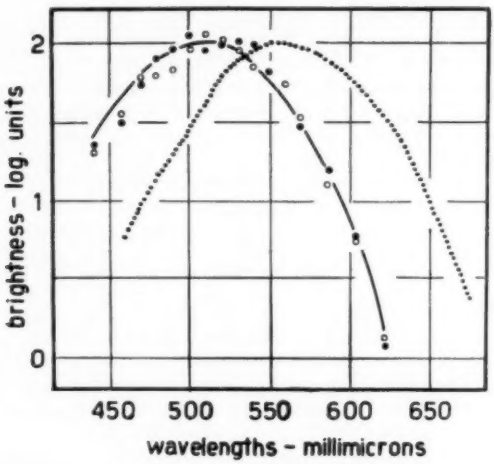

Fig. 2.—Visibility curves for E. O. (open circles) and A. O. G. (black circles). The ordinates represent the relative brightnesses of an equal energy spectrum. The solid line is the normal scotopic visibility curve; the dotted line is the normal photopic visibility curve.

SPECTRAL VISIBILITY

The relative brightness of spectral colors was studied for 2 of our subjects, A. O. G. and E. O. The apparatus used was the Helmholtz color mixer. This apparatus submits to the observation of the subject a divided circular field of light. The wavelength and intensity of the light in each half of the field can be separately controlled, the wavelength by means of prism monochromators and the intensity by means of crossed Nicol prisms and variable slits. The size of the circular field

used was 3 degrees. For the determination of the visibility curves we held constant the wavelength and intensity of the light in one half of the circular field. A different wavelength was exposed in the other half, and the subject was required to make a match merely by altering the intensity of the second light. In this manner, the relative brightnesses of light throughout the spectrum can be determined. For normal trichromatic subjects this procedure would be difficult and the results inaccurate, because the observed color differences would obscure the brightness differences; heterochromic photometry is notoriously difficult. With our achromatic subjects, however, this problem did not arise, for to them all spectral lights appeared similar and could be matched exactly by manipulation of intensity. A limiting factor in the accuracy of the data given by our subjects was their intensity discrimination, which was undoubtedly reduced (together with the visual acuity) by the absence of photopic vision. Nevertheless, by taking the averages of several readings at each setting satisfactory data were obtained. During the test the right half of the

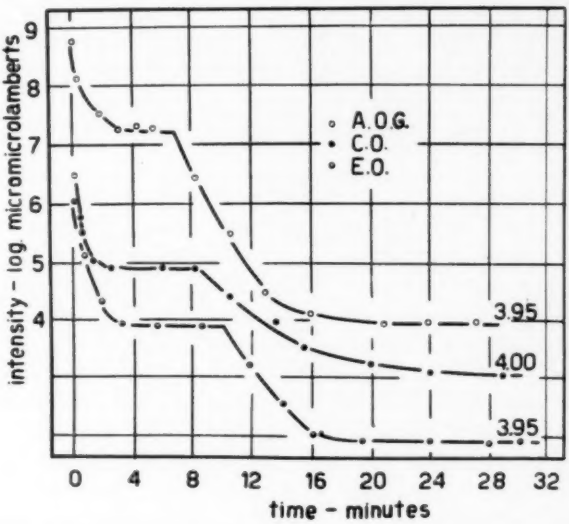

Fig. 3.—Dark adaptation curves given by our 3 subjects. The curve for A. O. G. is correctly placed on the ordinate axis. The curves for C. O. and E. O. have been moved down by 1 and 2 log units, respectively, in order that the curves may be studied individually. The correct thirty minute threshold is indicated for each curve. Measurements were made with natural pupils.[5]

light field was illuminated by green light at 500 millimicrons at an intensity well within the photopic range. In the region from 460 to 550 millimicrons settings of the second monochromator, illuminating the left half of the circular field, were made at every 10 millimicrons. Outside this range settings were made somewhat less frequently. The total spectral range studied was from 440 to 620 millimicrons. In the computation of the data corrections were made for the energy distribution of the light source. The brightness values given refer, therefore, to an equal energy spectrum.

The visibility curves of our 2 subjects are presented in figure 2. Here the solid line is the normal scotopic visibility curve, which may be obtained with a normal dark-adapted eye with low scotopic levels of illumination.[7] The dotted line is the

7. Hecht, S., and Williams, R. E.: The Visibility of Monochromatic Radiation and the Absorption Spectrum of Visual Purple, J. Gen. Physiol. **5**:1, 1922.

normal photopic visibility curve, obtained at higher levels of illumination, such as we used.[8] The curves have been replotted logarithmically. It can be seen that the data for both our subjects fit the scotopic curve fairly well, particularly in the ascending and descending limbs of the curve, where its separation from the photopic curve is most evident.

DARK ADAPTATION

Measurements of dark adaptation were made on the right eyes of all 3 subjects with the Hecht-Shlaer [9] adaptometer. The preadapting light intensity was 1,500 millilamberts, exposed to the eye for three minutes. The standard conditions were employed, a 3 degree violet test light being exposed for flashes of one-fifth second 7 degrees temporal to the fixation point. Fixation of the pupil or miosis was not employed.[5] Under these conditions, the normal dark adaptation curve shows two distinct portions, attributed to cone and rod adaptation.[10]

The curves for our subjects are reproduced in figure 3. They all showed two sections, with two distinct rates of dark adaptation. The first period of dark adaptation leveled off at intensity levels of 7.25, 5.95 and 5.95 log micromicrolamberts for the 3 subjects. The transition times between the two processes occurred at seven, eight and one-half and ten minutes. After thirty minutes the second stage of adaptation had leveled off at intensity levels of 3.95, 4.00 and 3.95 log micromicrolamberts, respectively. These figures do not differ greatly from those of the normal range.[10]

COMMENT

The subjects reported here showed complete color blindness for the entire visible spectrum, as was evident from their ability to match lights of any wavelength on the Helmholtz color mixer. They all showed diminished visual acuity, central scotomas, ocular nystagmus and photophobia. The 2 subjects whose visibility curves were determined showed evidence only of scotopic, or rod, visibility. The shape of the visibility curve is probably the most important single evidence in determining whether rod or cone vision is present, for it depends primarily on the absorption spectrum of the photosensitive pigment in the sentient cells. It is the absorption spectrum of rhodopsin (visual purple) which accounts for the shape of the scotopic visibility curve.[6] Similarly, it is thought to be the absorption spectrum of iodopsin, found in cone cells, which gives the photopic visibility curve its shape.[11] There is no instance in which visual purple occurs in cone cells and mediates photopic vision. It is inconceivable, therefore, that cone cells played a role in the visibility curves given by our subjects.

Nevertheless, the dark adaptation data showed clearly two distinct curves for each subject, similar to the curves which we customarily attribute to cone and rod adaptation. We had expected that the first curve would be missing and that only the second, or rod, curve would be present. This was the type of dark adaptation curve given by the subject of Hecht and associates [12] and by Sloan and Newhall's [2]

8. Gibson, K. S., and Tyndall, E. P. T.: The Visibility of Radiant Energy, Scientific Paper 475, United States Department of Commerce, Bureau of Standards, 1923.

9. Hecht, S., and Shlaer, S.: An Adaptometer for Measuring Human Dark Adaptation, J. Optic. Soc. America **28**:269, 1938.

10. Hecht, S., and Mandelbaum, J.: The Relation Between Vitamin A and Dark Adaptation, J. A. M. A. **112**:1910 (May 13) 1939.

11. Wald, G.: Photo-Labile Pigments of the Chicken Retina, Nature, London **140**:545, 1937. Chase, A. M.: Photosensitive Pigments from the Retina of the Frog, Science **87**:238, 1938.

12. Hecht, S.; Shlaer, S.; Smith, E. L.; Haig, C., and Peskin, J. C.: The Visual Functions of a Completely Color Blind Person, Am. J. Physiol. **23**:94, 1938.

subjects A. B. and J. W. One of our subjects, C. O., did give a single curve on one occasion; we were unable to repeat this, however. Similarly, the subject of Hecht and associates seemed to give a double dark adaptation curve on one occasion, which could not be repeated. Furthermore, their subject regularly gave double curves in intensity discrimination. This led them to make the suggestion that there may be two types of rod cells in the achromatic eye.

The double dark adaptation curves demonstrated by our subjects may similarly be explained by postulating the existence in such subjects of two types of rod cells, the visual purple regenerating more rapidly in one than in the other. This would be a valuable asset, for it would replace the rapid cone dark adaptation and thereby eliminate a prolonged period of relative blindness after the exposure to a bright light before the usual slow rod dark adaptation got under way. Hecht's subject seems to have become adapted to the situation by speeding up the entire range of rod dark adaptation to the speed of cone dark adaptation, despite the high levels of preadapting intensities. Another explanation for the double dark adaptation curves given by our subjects is the possibility that the peripheral areas of their retinas are not entirely devoid of functioning cones. It is conceivable that too few cones were present to affect the visibility curve but sufficient to take over the perception of light during the early period of dark adaptation, when the rod cells were completely inactivated because their visual purple had not yet regenerated significantly. Since the cone population seems to bear little relation to the cone light threshold,[5] it is possible that a small number of functioning cones could produce this effect. If this is the case, the few cones present are presumably identical with respect to color sensitivity and offer no basis for color discrimination.

NOTE.—Since this paper was prepared, one other achromatic subject, L. S., has come to the attention of one of us (J. M.). He shows the typical scotopic visibility curve. His dark adaptation curve shows only a faint suggestion of photopic function, the curve being predominantly scotopic in shape.

The spectral visibility of our subjects was measured at the Biophysics Laboratory at Columbia University. Dr. Simon Shlaer assisted in the use of the Helmholtz color mixer.

49 Pearl Street, Hartford, Conn.
258 Henry Street, Brooklyn.

THROMBOSIS OF CENTRAL RETINAL VEIN TREATED SUCCESSFULLY WITH HEPARIN

REPORT OF TWO CASES

CHARLES M. ROSENTHAL, M.D.

AND

JOSEPH T. GUZEK, M.D.

Resident in Ophthalmology, Brooklyn Eye and Ear Hospital

BROOKLYN

It is common ophthalmic knowledge that thrombosis of the central vein of the retina almost always leads to blindness. Often it results in intractable hemorrhagic glaucoma involving many unsuccessful operations and eventually leading to enucleation.

In a survey by Holmin and Ploman,[1] it was found that of 78 thromboses of the central retinal vein, the majority were branch thromboses. In only 13 patients was there complete occlusion of the trunk. Of these 13, who were treated by the usual conservative methods, 9 became totally blind—8 as a result of glaucoma and 1 as a result of retinitis proliferans. Of these 9, 5 required enucleation. Of the remaining 4 patients, who had no increase in intraocular tension, the vision improved in 1 to 6/21, in 2 to 6/60 and in 1 to perception of hand movements in the temporal region. Even in the patients with branch thrombosis, the results were poor. Of 26 patients followed for three months by Ploman,[2] 4 became worse, 12 remained unchanged and 10 improved slightly, with an average improvement in vision to 6/30. Thus it becomes evident that any procedure which affords a means of combating thrombosis of the central retinal vein and its branches is extremely desirable, for this condition is by no means rare.

The cases here reported are interesting from two standpoints—first, in the length of time during which the thrombosis existed before treatment (in one case five weeks and in the other three weeks) and, secondly, in the exceptionally good visual results obtained. It should be borne in mind that these were cases of trunk occlusion of the central retinal vein and not of branch block. As will be pointed out, in nearly all of the cases previously reported, treatment with heparin was begun almost immediately after the thrombosis had occurred, although in 5 cases of branch thrombosis an average of two and one-half weeks elapsed before treatment was instituted and in 1 case five months elapsed. Vision in the last-mentioned case improved from 6/60 to 6/21. Good visual results were obtained mostly in those cases in which the occlusion was of a branch. Even in these cases the results were only fair. The average improvement in vision was to 6/21, and the length of time it took averaged about two weeks. However, considering the poor results obtained prior to the use of heparin, the results obtained in these cases were worth while.

This paper was read in part before the New York Academy of Medicine, Section of Ophthalmology, May 18, 1942; a discussion of one of the cases appeared in the February issue of the ARCHIVES, page 334.

1. Holmin, N., and Ploman, K. G.: Thrombosis of Central Vein of Retina Treated with Heparin, Lancet **1**:664, 1938.

2. Ploman, K. G.: Heparin Treatment of Thrombosis in the Central Vein of the Retina, Acta ophth. **16**:502, 1938.

Holmin and Ploman [1] in March 1938 reported the first case in which heparin, an anticoagulant, had been used in the treatment of thrombosis of the central vein of the retina. An average of 1.66 mg. of heparin per kilogram of body weight was given intravenously every four hours during the day for eleven days. The vision improved from 6/30 to 6/7 in one week and to 6/6 in two months. It should be noted, however, that, while the thrombosis was in the trunk of the vein, the treatment was instituted within forty-one hours after the onset of the symptoms.

Rea [3] reported in April 1941 some of his results in the treatment of thrombosis of the central retinal vein by means of heparin. Of 5 cases, in 3 there was complete occlusion of the trunk and in 2 occlusion of a branch. In 1 case of complete thrombosis, treatment was entirely ineffective and the eye became blind. Of the other 2 cases, an unspecified amount of improvement occurred in one, and in the other vision rose from 2/60 to 6/24. In the 2 cases of branch thrombosis, complete cure resulted, the vision returning to 6/6. Rea did not give any further details.

REPORT OF CASES

CASE 1.—*History.*—F. C., a 39 year old white woman, a housewife, presented herself at the Brooklyn Eye and Ear Hospital Oct. 29, 1941 with the complaint of poor vision in the left eye. Five weeks previous to admission she had been free from ocular complaints, and she had never worn glasses. She was definite about the fact that vision had always been good in both eyes. She stated that five weeks before admission she had had the first of four episodes of flashes of light, or scintillating scotomas of which all but the last were transient. The last occurred four weeks prior to admission, after which her vision became blurred, and the spots before her eyes had not cleared up. These were described as being in the peripheral field of vision at first, and then gradually encroaching on the central field. In a week the whole visual field had become one big blur, or "spot" as she called it.

The family history revealed nothing important. Her father had died at the age of 55, the cause of his death being unknown. Her mother was living and well.

The patient had had measles, mumps and pertussis during infancy. She had had one severe postpartum hemorrhage at the age of 20. At the age of 27, she had a vaginal plastic operation with repair of the cervix. Since the age of 29 she had had no medical treatment and had been in good health.

Examination.—On physical examination, the blood pressure was found to be 124 systolic and 72 diastolic. The temperature, pulse rate and respiratory rate were normal. No cardiovascular disease was found. The heart was normal in size, and the sounds were regular and of good quality. There were no murmurs. The medical consultation gave essentially negative results. There was no evidence of systemic disease. Examination of the nose and throat by an otolaryngologist showed that some pus could be expressed from the right tonsil. The tonsils were considered as a focus of infection. Roentgenograms of the sinuses showed some clouding of the left antrum. Dental studies gave entirely negative results.

The Wassermann reaction was negative. Examination of the blood gave the following values: red cells 4,870,000, hemoglobin content 84 per cent, color index 0.89, white cells 6,850, differential count normal, bleeding time one minute and coagulation time one minute. The urine was normal except for slight traces of albumin. The blood chemistry was normal, as was the stool.

Ocular Examination: Vision was 6/4 —2 in the right eye and 2/60 in the left. The periorbital structures were normal. The conjunctivas, corneas and scleras showed no pathologic change when examined by the usual methods. The anterior chambers were normal. The pupils measured 5 mm., were round and reacted well to light directly and consensually, in accommodation and to convergence. In neither eye did the iris, lens or vitreous show any abnormalities.

Examination of the right fundus revealed that the disk was round and had clearcut edges. The vessels were of 3:2 ratio. There was a normal light streak on the retinal vessels. There was no evidence of any arteriovenous compression and no evidence of hemorrhage or exudates. The macula was normal in appearance.

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3. Rea, R. L.: Treatment of Thrombosis in the Central Vein of the Retina with Heparin, Arch. Ophth. **25**:548 (April) 1941.

Examination of the left fundus disclosed that the entire retina was covered by large and small hemorrhages. Some were round and others flame shaped. It looked as though the retina had been splattered with a red paint brush. It had the typical textbook appearance. The veins were markedly dilated and tortuous and in some places were lost from view because of the intense edema. The disk was hardly visible owing to intense edema and could be made out only by the emergence of the vessels. The macular region was covered by numerous hemorrhages.

The peripheral fields were normal with a 3 mm. white test object. In the central fields a 26 by 32 degree central scotoma could be elicited.

Treatment.—After a complete study and work-up, and not until about twenty-six hours after admission, treatment was instituted. Heparin was administered intravenously and as a local prophylactic measure 1 per cent pilocarpine nitrate solution was instilled three times a day in the left eye.

The first dose of heparin was 20 cc. in 1,000 cc. of 5 per cent dextrose in saline solution, and four hours after completion of this injection, 10 cc. in 500 cc. of saline solution was given for two doses. Ten cubic centimeters contains 100 mg. of the purified sodium salt of heparin.

The coagulation time was tested by the capillary tube method regularly four hours after each injection throughout the treatment. It now varied between twenty-two and forty minutes. The dose was reduced to 5 cc., and the heparin was given undiluted directly into the vein at four to four and one-half hour intervals for fourteen injections. The coagulation time four hours after each injection varied from seven to nineteen minutes. After this, the dose was decreased to 4 cc. every five hours, to 3 cc. every six hours, to 2 cc. every six hours and, finally, to 2 cc. every eight hours. A total of 180 cc. of heparin was given in ten days by this intermittent intravenous method.

Course.—The patient was confined to bed. On the third day a few of the obscured arteries became visible. Incidentally, the menstrual flow was not altered when it occurred on the third day.

On the fourth day, the veins were somewhat reduced in size, and the hemorrhages appeared to be becoming absorbed.

On the twelfth day, the borders of the disk could just be made out. The retinal edema had subsided considerably. The veins were still distended. Much more of the arteries was visible. There were still some hemorrhages in the macula.

On the eighteenth day, the outlines of the disk were distinct and the retinal edema much less.

On the twenty-sixth day, the entire fundus appeared almost normal, except for small hemorrhages still present in the macular region.

One month later, there was only one small hemorrhage left in the macular region, and this had completely disappeared several weeks later.

The progress of the visual acuity was as follows: Oct. 30, 1941, 2/60; November 2, 6/60; November 6, 6/30 + 1; November 15, 6/21; November 25, 6/15 — 1; Jan. 23, 1942, 6/15, and April 7, 1942, 6/7 — 2 + 2, with correction.

CASE 2.—*History.*—E. H., a white woman aged 35, complained of blurring of vision of the left eye. Three weeks prior to her admission to the Long Island College Hospital on Sept. 14, 1941, she awoke in the morning with a "fluff" over her left eye as though she were looking through a white cloud. This cloud was continuously present but seemed to be worse when she was out in the sun. She had no other ocular complaints. She had some pain in the back of her neck and head for three days.

Her family history revealed nothing significant. She had had scarlet fever as a child, contracted typhoid fever at the age of 11 and had her tonsils and adenoids removed at 15. There was a history of renal trouble during her pregnancy six years later. She had had one spontaneous abortion. During her last two pregnancies she had hypertension, edema of the ankles and dyspnea but no convulsions.

She had had a sudden attack of dizziness and blurred vision, which lasted only two or three minutes, about three months before and a similar attack about three weeks later. She had frontal headaches at approximately two week intervals for one year.

Examination.—On her admission to the Long Island College Hospital, examination disclosed that vision was 6/21 in the right eye, corrected to 6/9 —3, and 6/15 — 3 in the left eye, with improvement impossible. Complete external ocular examination gave negative results. The pupils measured 5 mm. and reacted to light and in accommodation. The intraocular tension, the lens and the vitreous were normal in each eye. The fundus of the right eye was entirely normal. However, examination of the left fundus showed that the disk was blurred nasally,

superiorly and inferiorly, owing to edema. There were many hemorrhages on the disk. The macula was covered by numerous flame-shaped hemorrhages. The veins were markedly dilated, irregular and sausage shaped. The arteries were extremely narrow and very pale. There was marked arteriovenous compression. The veins seemed to be buried in the retina in places. The large flame-shaped hemorrhages seemed to cover almost the entire fundus. The final diagnosis was thrombosis of the central retinal vein of the left eye.

The vision of the right eye had been poor for many years. Studies of the central field revealed, by angioscotometry, a small central scotoma. The reason for the amblyopia of the right eye could not be fully explained.

Physical examination by the medical department showed no abnormalities. The heart and lungs were normal. Gynecologic consultation showed no pathologic change. Dental consultation also gave negative results.

The peripheral fields were normal with a 3 and a 1 mm. white test object. Roentgenograms of the chest, skull and sinuses revealed nothing abnormal. A blood count showed only slight secondary anemia. Urinalysis, a Wassermann test and chemical examination of the blood gave essentially negative results. The bleeding time was five minutes, and the clotting time was one and one-half minutes.

Treatment.—After complete study of the patient, treatment with heparin was begun.

On September 15, 200 mg. of heparin in the form of undiluted solution of the purified sodium salt was given intravenously. On the following day, 125 mg. was given in the morning and in the evening. However, the patient afterward had severe bleeding from a socket from which the tooth had just been extracted. This compelled us to withhold the treatment until September 21, when it was resumed. The heparin was then given for four days, 125 mg. in the morning and in the evening. Thus, a total of 250 mg. of heparin was given each day for six days. The treatment was completed on September 25. The patient was discharged to the clinic on October 1.

Course.—On September 19, the vision in the left eye was reduced from $6/15 - 3$ to $6/21$. This was after only three doses of heparin had been given. Less than three weeks later, absorption of the hemorrhages throughout the fundus was noticeable. The vision in the left eye had improved to 6/15.

On November 18, it was noted that the papilledema was much less. Blurring was present only on the nasal border. The veins were still engorged, and the hemorrhages were practically all absorbed except a few small punctate hemorrhages. Vision at this time was 6/9.

On December 16, less than two months after the beginning of treatment, the fundus was practically normal in appearance except for slight tortuosity of the veins and occasional flame-shaped hemorrhages in the upper temporal field. Vision in the left eye was $6/9 + 3$. The intraocular tension had consistently been normal.

On December 30, only one small punctate hemorrhage, superior to the macula, was noted. The vision was $6/6 - 3$.

On January 6, the fundus was entirely normal. The vision was 6/6.

The peripheral fields were always within normal limits. The central fields showed a large central scotoma of 30 degrees, which gradually decreased to a small tonguelike centrocecal angioscotoma and finally disappeared entirely.

COMMENT

It would appear from the reports in the literature that treatment with heparin when instituted early gives excellent results.

In this paper 2 cases are presented. In the first one, five weeks elapsed between the occurrence of the thrombosis of the central retinal vein and the beginning of the treatment with heparin. In the second case, only three weeks elapsed. In both cases vision of 6/6 was finally obtained.

These results would seem to indicate that thrombosis of long standing is also amenable to treatment. The reason is difficult to understand. However, it may be that the heparin prevents further increase in the thrombotic process, thus permitting greater canalization and resumption of the normal function of the vein.

142 Joralemon Street.

CHOLESTEATOMA OF ORBIT

G. M. CONSTANS, M.D.
BISMARCK, N. D.

In discussing cholesteatoma of the orbit one is immediately struck by the scarcity of reports of cases. Although somewhat closely allied to dermoid cyst of the orbit, cholesteatoma is a distinct entity. As noted by Samuels, dermoid cyst of the orbit is rare; this is a truism. Likewise, cholesterol in a cyst of the orbit is exceedingly rare, while so-called true cholesteatoma of the orbit is even less frequently encountered. The purpose of this paper is to define cholesteatoma of the orbit, present the theories as to its etiology and classification, review the cases reported in the literature and report a new case.

A number of cases of dermoid cyst of the orbit and of cholesteatoma of the paranasal sinuses, mastoid, etc., have been reported. These will not be reviewed except as to their general characteristics and the manner in which they differ from true, or primary, cholesteatoma of the orbit.

To date I have been able to collect reports of 15 cases of cholesteatoma of the orbit, as follows: Kreibig, Marino Varona, Rohmer, Gosselin, Spencer, Schirmer, Teplovskiy, Demarquay, Michàil, Panneton and Rintelen 1 each and Pincus and Birch-Hirschfeld 2 each. The case to be reported here brings this number to 16. However, if one adheres to Birch-Hirschfeld's classification, or requirements of a true cholesteatoma of the orbit, there are only 5 proved cases—those of Rohmer, Schirmer, Birch-Hirschfeld, Michàil and Panneton.

The stipulations of Birch-Hirschfeld are that (1) true cholesteatoma possesses no inflammatory wall, (2) it is located subperiosteally in the orbit and (3) it contains or is composed of cholesterol.

Rintelen stated that the subperiosteal location is not an essential characteristic and that, as in Michail's case, the cyst may even have an epithelial lining. Also, owing to pressure in growth it may be between the remaining periosteum and bone. In this he contends that Birch-Hirschfeld's criteria may fail, and he bases his diagnosis on the construction and character of the cyst. At the same time he admits that both his case and the cases of Pincus are not instances of true cholesteatoma or even of pseudocholesteatoma, calling them cases of dermoid cyst with cholesterol crystals.

It is well to maintain some standard of comparison, even if a somewhat arbitrary one, when dealing with a congenital growth. The case to be here reported does meet Birch-Hirschfeld's criteria; furthermore, so far as can be ascertained, the patient is one of the youngest in whom this disease has been recorded. The case brings the total cases of true cholesteatoma of the orbit to 6.

The causation is, of course, speculative. It is generally conceded that true dermoid cyst and cholesteatoma are not due to trauma, but are developmental aberrations, although they may not be manifested until later in life, and that they tend to grow larger at puberty.

Ida Mann stated that all ocular and orbital abnormalities can be classified in three groups: those due to simple arrest of development, pure aberrations and

From the Department of Ophthalmology, Quain and Ramstad Clinic.
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those that are due to an arrest but have a subsequent aberrant growth. She further divided them according to five periods of development from organogenetic to postnatal.

Thus, in discussing congenital tumors of the orbit, of which the dermoid is one type, she stated that they fall into one of three classifications: (1) tumors of one germ layer, such as osteoma, angioma and nevi; (2) tumors of both mesoderm and ectoderm (including dermoid cyst and, of course, cholesteatoma of the orbit) and (3) tumors of three germ elements (that is, true malignant teratoma).

It is with the second class that I am here concerned. Most dermoid or oil cysts of the orbit would fall in this class, as would those with cholesterol, pseudocholesteatoma and true cholesteatoma of the orbit. Collins and Mayo, in discussing aberrations in the development of the eye, stated that such cysts are most often found along the line of the orbitonasal fissure. They are congenital, are often first manifested at puberty and are most commonly found at the upper and outer angle of the orbit. These authors stated that in early embryonic life the covering of the dura and the head are in contact but with the formation of the cranial bones become separated, remaining in contact longest in the line of sutures. Thus, should a piece of epidermis adhere to the dura, it might become cast off with some of its epithelium and thus be sequestered and form the start of a cystic growth. When such cysts are found, they interfere with the formation of bone and hence the occurrence of a bony depression beneath them. Heimendinger, in referring to the paranasal sinuses, stated that true cholesteatoma is always a disturbance of evolution during embryonic life. Skillern and Spencer concurred in this opinion.

Referring to dermoid cysts of the lids, Whitnall stated that they often lie beneath the orbicularis oculi muscle and may hollow out the frontal bone or even be connected with the dura. His explanation is that they are caused by inclusion of the epiblast between the growing bones.

Mann called it an error to explain "dermoid formation" on the assumption that the maxillary process is covered by ectoderm and is applied to the ectoderm of the head. The bony walls of the orbit are formed from condensations in both the maxillary and the visceral mesoderm. The associated paraxial mesoderm gives rise to the upper and inner walls of the orbit, while the visceral mesoderm (maxillary process) forms the lower and outer walls of the orbit and structures below and behind the eye.

Aschoff in his book on pathologic anatomy gave a good description of cholesteatoma: "It is often round and white, with a silklike sheen, consisting of dry, brittle elements densely packed in fine layers, usually with a connective tissue capsule. It probably originates from developmental causes, with inclusion of epidermis, and is similar to congenital dermoid cyst."

Other types due to inflammatory reaction, such as those found in mastoiditis or sinusitis, are common. The tumor in Spencer's case no doubt was of this class, as there was a history of infection involving the frontal sinus. Trauma may cause such tumors when epidermal elements are carried into the wound.

The first, or developmental, type would be the primary cholesteatoma considered here.

Thus, it may be seen that whatever theory is given, all authorities agree that dermoid cyst and cholesteatoma of the orbit are formed congenitally, owing to a separation or segregation of the elements forming the orbit; that there is an increase in growth at puberty, and that the two types are genetically similar. There seems to be no doubt that they are tumors of both mesoderm and ectoderm.

Possibly, as Rintelen noted, cholesteatoma of the orbit is not a true tumor or a formation differing essentially from dermoid or epidermoid cyst. However,

it would seem logical and convenient, especially on account of its rarity, to classify it, as do Johannes Müller and Birch-Hirschfeld, as a separate entity, that is true, or primary, cholesteatoma of the orbit.

Such a concept of cholesteatoma is purely morphologic, and the criteria to be followed are the characteristic structure of the tumor and its cystic content, and these are, of course, operative findings. Thus, one must note the differences in these respects, even though they may be empiric, between a dermoid and cholesteatoma.

Of the cases previously reported, those of Kreibig, Marino Varona, Gosselin, Teplovskiy, Dermarquay, Rintelen and Pincus would seem to come into the general classification of cholesteatoma of the orbit, though not strictly in the Birch-Hirschfeld classification. The tumor in cases like those of Spencer does not conform to the requirements of a primary tumor of the orbit, chiefly because the growth does not arise in the orbit but is an extension or involvement from the paranasal sinuses.

Pincus noted that in his cases the tumor was not a dermoid, though possibly it should be called pseudocholesteatoma of the orbit. As Rintelen stated, there are undoubtedly dermoid cysts of the orbit that are subperiosteal; he expressed the opinion that the Birch-Hirschfeld criteria fail at times and that the diagnosis depends on the contents of the cyst. In his excellent review in 1934 of 6 previously reported cases, he concluded that only in those of Rohmer, Schirmer, Birch-Hirschfeld and Michàil did the tumor meet the requisites of primary cholesteatoma of the orbit. In this I agree, although it is difficult to pass on these cases. To them should be added the recent case reported by Panneton.

These cases can be noted in the accompanying table, in which the salient features are outlined. Some of the data are insufficient owing to the paucity of the report or the impossibility of obtaining the original article at this time. It will be noted that the first case was reported in 1860 and that 9 patients were males, 3 females and the sex of 4 not noted. The age varied from 9 to 55 years, and the duration of the tumor varied from two to thirty-four years. In all cases exophthalmos was present; pain was uncommon and not reported in any of the cases of primary cholesteatoma. Roentgen examination was of great value and postoperative recovery the rule. The finding of cholesterol was, of course, universal in these cases. Cases in which there was sinus involvement are not considered, though Spencer's case is listed. As noted by Kreibig, the diagnosis of orbital tumor is often difficult, and the conditions giving a similar roentgenologic picture to that of cholesteatoma of the orbit are subperiosteal hematoma and mucocele. The clinical picture of cholesteatoma is that of gradual increase in exophthalmos without pain and with extensive destruction of the bony wall of the orbit or its margin.

I wish to add to this series the following case:

V. K., a schoolgirl aged 17, presented herself on Nov. 26, 1941 for observation. Her complaint was protrusion of the left eye. Although she thought the eye had been nearly normal in position at times, it was generally proptosed. During the past year the proptosis had increased, but there had been no change in the eye as to vision, movement or pain, nor had headache been noted. The chief complaint was the unsightly appearance of the eye, and this was the reason for the patient's seeking medical aid.

She had first been seen on July 30, 1936 in the ophthalmic department of the Quain & Ramstad Clinic, her age then being 12 years. Her parents brought her in because they thought her left eye was larger than her right. They had first noted this condition about six months previously and were of the opinion that it had since increased. Four months before she was brought to the clinic the child was given glasses, which did not alter her condition or appearance. Her general health had always been good. She was mentally active and in the sixth grade in school.

Summary of Reported Cases of Cholesteatoma of the Orbit

No.	Author	Year	Patient		Location of Tumor	Trauma	Inflammation	Exophthalmos	Duration, Years	Visual Acuity	Roentgenologic Change	Pathologic Changes	Result	Classification (Birch-Hirschfeld)
			Age	Sex										
1	Demarquay.....	1860	33	♂	Upper orbital wall	No	No	Yes	10	Not given	Not given	Fluid with cholesterol	Post-operative fistula	Secondary cholesteatoma
2	Rohmer.....	1889	..	..	Orbit	No	No	Yes	Not given	Not given	Not given	Cholesteatoma	Good	Primary cholesteatoma; cited by Birch-Hirschfeld
3	Schirmer.....	....	..	..	Orbit	No	No	Yes	Not given	Not given	Not given	Cholesteatoma	Not given	Primary cholesteatoma; cited by Birch-Hirschfeld
4	Gosselin.....	....	..	..	Orbit	....	....	Yes	Not given	Not given	Not given	Cholesterol	.....	Secondary cholesteatoma
5	Teplovskiy.....	....	..	..	Orbit	....	....	Yes	Not given	Not given	Not given	Cholesterol	.....	Secondary cholesteatoma
6	Pincus.....	1927	45	♂	Left orbit	No	Yes	Yes, forward and down	Several	Not given	Dehiscences and bony thickening	Cholesterol	Relapse	Secondary cholesteatoma
7	Pincus.....	1932	46	♂	Not given	No	Yes	Yes	Not given	Not given	Bony pressure changes	Cholesterol	Good	Secondary cholesteatoma
8	Birch-Hirschfeld	1930	32	♀	Not given	No	No	Yes	6	Not given	Not given	Cholesteatoma	Good	Primary cholesteatoma
9	Birch-Hirschfeld	1930	17	♂	Left orbit	Yes	Yes	Yes	17	6/18	Normal	Cyst with fluid and crystals	Good	Cyst with secondary cholesteatoma
10	Spencer.....	1930	40	♂	Right orbit and frontal sinus	Yes	Yes	Yes, out and down	34	2.5%	Cloudy sinuses	Pus, cholesterol and detritus	Fair	Secondary cholesteatoma of sinuses and orbit
11	Michail.....	1930	9	♂	Right eyebrow	No	No	Yes, down and nasal	8	5/30	Rarefaction, upper and outer angle of orbit	Cholesteatoma, no wall	Slow healing	Primary cholesteatoma
12	Rintelen.....	1934	31	♂	Right orbit	No	Yes	Not given	Not given	Not given	Not given	Dermoid cyst with cholesterol and inflammatory material	Good	Cyst with secondary cholesteatoma
13	Marino Varona.	1937	29	♂	Upper sulcus, right	Yes	Yes	Yes, slight, down	2	Not given	Triangular area of rarefaction, upper external angle of orbit	Capsule: 1 part epithelioid, 1 part dermoid with cholesterol	Slow healing	Secondary cholesteatoma with inflammation
14	Kreibig.....	1938	55	♂	Orbital margin, left	No	Yes, frontal sinusitis	Yes, down and out	32	6/6	Left upper orbital margin gone	Cholesterol	Good	Secondary cholesteatoma
15	Panneton.....	1941	35	♀	Left orbit	No	No	Yes, down and out	34	4/10	Defect and thickening of bone	Cholesteatoma	Good	Primary cholesteatoma
16	Constans.....	1942	17	♀	Left orbit	No	No	Yes, out	5	6/6—4	Multiloculated cystlike tumor with destruction of part of orbital wall	Cholesteatoma	Good	Primary cholesteatoma

The family history in general was irrelevant. The father and mother were living and well, and there was no illness among the brothers and sisters.

The patient's vision was 6/6 — 1 in each eye without correction and 6/6 in the right eye and 6/6 — 1 in the left eye with correction. She was wearing a + 0.25 D. sph. before the right eye and a + 0.50 D. sph. before the left eye and could read American Medical Association 14/24.5 type at 25 cm. readily with each eye with and without correction. Externally the eyes appeared normal in size but not in shape or position. There was an evident proptosis of the left eye, with an apparent enlargement of the eye due to a widening of the palpebral fissure. There was a depression temporally between the globe and the lower lid in the left eye. The lids opened and closed freely, and the ocular movements were unimpaired. The pupils were round and regular and reacted to light and in accommodation and convergence. The tension seemed normal on palpation, the fields were normal on rough testing and the cover test gave negative results. No palpable masses could be made out. Measurements with the Hertel exophthalmometer were 20 and 24 mm. The conjunctivas and corneas were clear,

Fig. 1.—Multiloculated cystlike tumors in the lateral wall of the left orbital cavity with two areas of fine absorption.

and the pupils dilated well in response to cocaine. The media were clear and the fundi essentially normal, although the left fundus showed a little haziness about the disk margin. No hemorrhages, exudates or detachments were noted.

The patient was referred for otorhinolaryngologic examination, and the report was as follows: The nose showed a slight deviation of the septum. There was a small midline scar in the skin of the upper lip. The tonsils had been removed surgically. In the postnasal space adenoid tissue was present. The external auditory canals and tympanic membranes were normal in appearance. The sinuses transilluminated well.

Roentgen examination showed the sinuses and the right orbit to be normal. A multiloculated cystlike tumor was evident in the lateral wall of the left orbital cavity. This projected into the orbital cavity and showed two rounded areas of bone absorption in the wall itself, each about 10 by 12 mm. in diameter. Oblique views showed this tumor apparently covered by a thin layer of bone. The diagnosis was tumor of the lateral wall of the left orbit, a possible osteochondroma (fig. 1).

The parents were unable to remain longer in town on account of the pressure of work on the ranch but were to bring the child back in one week for a more thorough investigation

and possible operation. However, they did not return for nearly a year, reporting to the medical department of the clinic on Nov. 8, 1937. They had been and still were in financial difficulties. The patient was seen in consultation. The vision was 6/6 —2, and there had been no apparent change in the proptosis or in the eyes externally since the year before.

Roentgen examination showed the previously described tumor in the left orbit with no essential change since the last examination. The diagnosis was tumor of the left orbit, and operation was again advised.

The patient did not remain and was not seen again until four years later, Nov. 26, 1941. The eye was more prominent than it had been. The father stated that at times the eye had been well within the orbit and a mass noted temporally, but when the eye protruded the mass was not seen. During the past year the eye had always been proptosed. The vision and general health had been good, and there was no pain.

The vision in the right eye was 6/6 —2 and in the left eye 6/6 —4, and the patient read American Medical Association type 14/24.5 at 31 cm. without correction. Externally the right eye appeared normal. The left was markedly proptosed outward. The left lids were thinned out, but covered the eye. With the Hertel exophthalmometer at 115, the measurements were

Fig. 2.—Preoperative photographs, taken Nov. 26, 1941, showing proptosis of the left eye, thinning of the lids, widening of the palpebral fissure and a temporal depression between the globe and the lower lid. The proptosis measured 13 mm.

21 mm. for the right eye and 34 mm. for the left; that is, a proptosis of 13 mm. was present in the left eye (fig. 2). The ocular movements were fairly good. The lids could be pushed back and the left eye nearly dislocated from the orbit. Palpation disclosed a mass in the outer portion of the orbit between the globe and the rim, apparently firmly attached as far back as one could palpate. It had the feeling of angleworms, though it was rather firm. There was no pulsation and no bruit. Near the fornices the left globe was somewhat hyperemic. The pupils dilated well in response to 1 per cent homatropine hydrobromide. The media were clear, and the right fundus was normal. The left fundus revealed the following changes: The superior nasal portion of the disk was blurred with papilledema of about 1 D. The vessels were normal in size, but were tortuous, and the macular region was normal. The perimetric fields were normal for form and color, with a slight enlargement of the blindspots, shown by Lloyd's campimeter, not considered pathologic.

Roentgenograms were made and the films compared with those taken in 1936 and 1937. Previously the tumor had consisted of two distinct parts, an upper area surrounded by some dense bone and a lower rarefied area in the floor of the orbit. Since 1937 the upper part had enlarged approximately 50 per cent and the lower part approximately 300 per cent. The

diagnosis was tumor of the left orbit with considerable enlargement since the last examination (fig. 3). Roentgen examination of the pelvis for generalized cystic disease of the bone gave negative results.

The girl was large, obese and overdeveloped for her age, apparently having a glandular dyscrasia. The general physical examination in the department of internal medicine gave negative results except to disclose a slight systolic heart murmur heard at the base. The blood pressure was 110 systolic and 70 diastolic. The lungs and abdomen were normal. The urine showed a specific gravity of 1.032, an acid reaction, a trace of albumin, no sugar, an occasional red blood cell and a few pus cells. The hemoglobin content was 97 per cent and the white cell count 12,950, with polymorphonuclear leukocytes 88 per cent, lymphocytes 11 per cent and metamyelocytes 1 per cent. The Wassermann reaction of the blood was negative. The basal metabolic rate was + 16. On surgical consultation a bilateral diffuse enlargement of the thyroid with no nodules and no evidence of hyperthyroidism was noted.

A diagnosis of tumor of the left orbit was made. On November 28, the patient was admitted to the Bismarck Evangelical Hospital for surgical intervention and for preliminary medication with sulfadiazine (2-[paraaminobenzenesulfonamido]-pyrimidine.

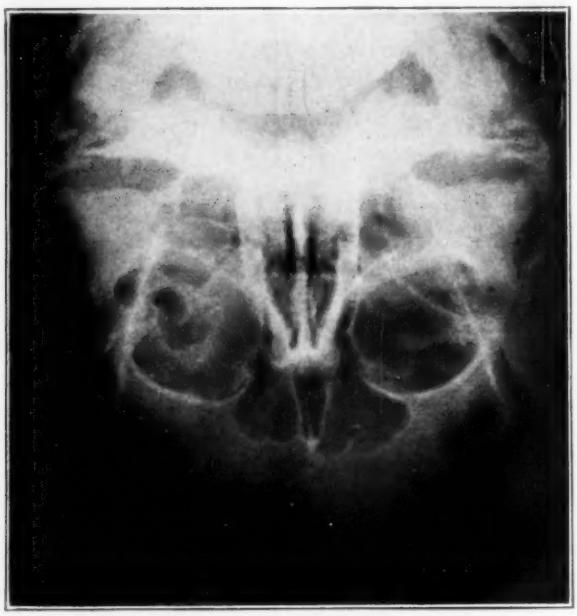

Fig. 3.—Enlargement of the two distinct parts of the tumor mass shown in figure 1, the upper enlarged 50 per cent and the lower 300 per cent over its previous size.

On December 1 a tumor of the left orbit was removed with the patient under intratracheal ether and nitrous oxide anesthesia. The incision was started in the region of the eyebrow about the middle third and extended downward about 4 mm. beyond the rim of the orbit temporally over the edge of the malar bone. It was continued down to the periosteum, which was incised and reflected back and down on the inside of the orbit, where it becomes the periorbita, being kept outside of the lacrimal gland until the apex of the orbit had been nearly reached. When this was dissected partly free, a large necrotic whitish mass very much like the material in a sebaceous cyst was encountered. No true wall or capsule was seen. It was felt that it was best not to cut through the periorbita, for it appeared that the mass was between it and the bony part of the orbit. Thus, the eye and the muscle cone were left intact except in two places, where the bony part of the orbit had been so eroded and sharpened that spicules had pushed through the periorbita and orbital fat had protruded slightly. All of this soapy material, which filled a 1 ounce (30 cc.) graduated glass, was removed. It was found that the growth had eroded the bony wall of the orbit, apparently while the orbit was growing, so that the bony part was filled with dehiscences and concavities, many ridges of sharp bone overhanging part of it. These occurred chiefly from the outer upper third to the lower half of the orbit and were smoothed off. The globe and muscle cone were replaced in the orbit, from which they had been pushed over nasally for removal of the aforementioned

mass. The eye then resumed its normal position in the orbit. The periorbita was sutured with interrupted catgut sutures, two stay sutures were placed in the fascia and the skin was closed with interrupted silk sutures. A petrolatum dressing was applied over the area of the wound. Atropine sulfate and White's ophthalmic ointment [1] were instilled between the lids and the wound bandaged. No hair, teeth or similar material was found in the mass removed, although crystals were present.

Fig. 4.—Photomicrograph showing laminated amorphous material without cellular structure.

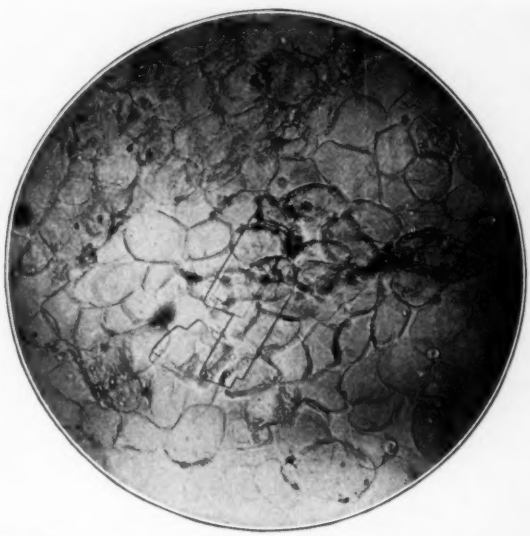

Fig. 5.—Photomicrograph of a wet mount showing cholesterol crystals and desquamated epithelial cells.

The pathologic report was as follows: "The specimen consisted of greasy fragile material, the nature of which could not be determined grossly. It contained numerous cholesterol crystals. A definite cyst wall could not be determined grossly. Histologic examination

1. Mercury bichloride 1:3,000 and sodium chloride 5:3,000 in petrolatum ⅛ ounce (3.5 Gm.)

Fig. 6.—Postoperative photographs (May 7, 1942) showing the absence of proptosis, slight widening of the palpebral fissure, the slight scar and the normal position of the globe.

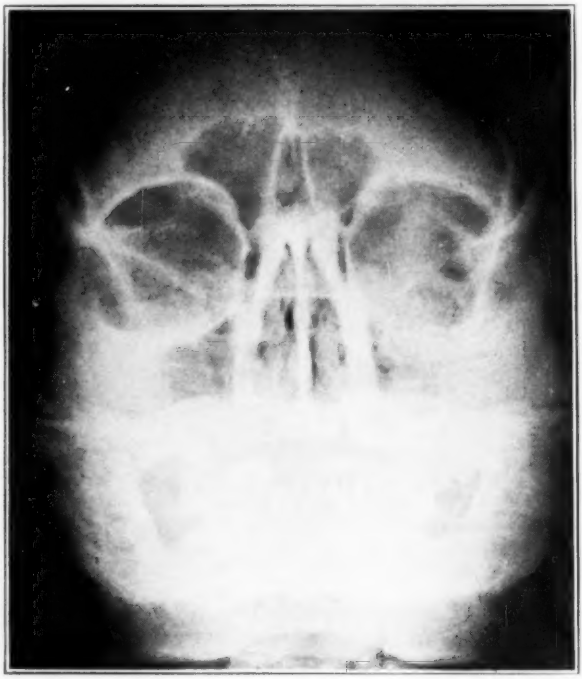

Fig 7.—Roentgenogram taken Oct. 14, 1942. There is no evidence of recurrence.

showed concentrically arranged laminations of a waxy material. Nuclear material was absent, but cholesterol crystals were present. The tumor appeared to be cholesteatoma. There was no tissue present which could be recognized as a cyst wall. The pathologic diagnosis was cholesteatoma of the orbit" (figs. 4 and 5).

The patient made an uneventful recovery and was dismissed from the hospital fourteen days later. The wound was healed; there was slight proptosis of the globe, but no diplopia, and the fundus was normal. The final diagnosis was primary cholesteatoma of the left orbit.

The patient was seen at frequent intervals after the operation, the last visit being on Oct. 14, 1942. She had been working at home, carrying on a normal life and had had no trouble in any way. The scar was scarcely visible. There was no proptosis and the cosmetic result was excellent (fig. 6). A roentgenogram of the orbit showed two bony defects in the region of the orbital wall where the tumor was removed, but no evidence of a recurrence of the growth was noted either roentgenologically or clinically (fig. 7). The vision was 6/6 in both eyes without correction, and the patient could read American Medical Association type 14/24.5 at 30 cm. readily. The measurement with the Hertel exophthalmometer set at 117 was 19 mm. for each eye. Although she had had some muscle imbalance for a month or so after the operation, there was none evident during her last visits, and there was no diplopia with the red glass test. There was no limitation of the ocular movement, and the fundi were essentially normal, although there was a slight tortuosity of some of the vessels in the left fundus.

SUMMARY

In reporting on this unusual condition I have endeavored to give the theory which might account for it, that is, that it is a congenital growth, no doubt from both mesoderm and ectoderm.

The criteria of true cholesteatoma of the orbit are that it possesses no inflammatory wall, is located subperiosteally in the orbit and contains or is composed of cholesterol crystals.

Not all of the previously reported 15 cases fit definitely into this classification, although I think they should be reported and listed. Five do, in my judgment, qualify as cases of true primary cholesteatoma of the orbit. To these I have added the case of true primary cholesteatoma of the orbit here reported, which makes 6 cases conforming to Birch-Hirschfeld's classification.

The tumor in my case was definitely congenital, there being no history of trauma and no evidence of an inflammatory mass. The age, between 11 and 12 years when the patient was first observed, is one of the youngest reported. There was definite erosion and absorption of the bony orbital wall. The mass was located subperiosteally in the orbit without a wall and contained laminated areas of cholesterol crystals.

Since operation the patient's appearance has been normal cosmetically, and she has an excellent functional result, with no proptosis, diplopia or muscle imbalance and with normal vision and fundi.

221 Fifth Street.

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ASTIGMATIC ACCOMMODATION

M. W. MORGAN JR., PH.D.

JACK MOHNEY, M.S.

AND

J. M. D. OLMSTED, PH.D.

BERKELEY, CALIF.

There has been a very great deal written, dating from the time of Dobrowolsky (1885), but more especially within recent years, about the so-called dynamic lenticular astigmatism or astigmatic accommodation. There is, however, no scientific foundation for the claim that the accommodative effort of the ciliary muscle deforms the lens unequally on different meridians . . . all the evidence goes to show that if any part of the ciliary muscle contracts in life, it contracts equally all round.[1]

Contrary to this statement of Duke-Elder, there is at least one report in the literature showing that astigmatic accommodation is a possibility. Grossman[2] found that in the cat physostigmine caused more active positive accommodation in the vertical meridian, by 5.00 D., than in the horizontal meridian.

Since 1939 we have been investigating the nervous control of accommodation.[3] During this time we have refracted the eyes of several hundred animals under different experimental conditions. The animals included were cats, rabbits, dogs, guinea pigs, rats and monkeys. In addition, a series of experiments were conducted on human subjects.[3b] The refractive state in this experimental work has been determined generally by skiascopy, but we have also photographed the Purkinje-Sanson images as well as the profile of the cornea and the lens, using the method described by Fincham.[4] Our results may be summarized in few words as follows: We have found that accommodation is reciprocally controlled by the parasympathetic and sympathetic nervous systems. When the cervical sympathetic nerve is stimulated the eye becomes more hypermetropic; on the contrary, when the oculomotor nerve is stimulated the eye becomes more myopic.

In approximately 90 per cent of the cats we investigated, the change in dioptic power of the lens on stimulation of the cervical sympathetic nerve was about 1.50 D.,

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From the Division of Physiology of the University of California Medical School.

1. Duke-Elder, W. S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1938, vol. 3, p. 759.

2. Grossman, K.: Further Investigations on Accommodation, Ophth. Rev. **23**:1, 347, 1904.

3. (*a*) Olmsted, J. M. D., and Morgan, M. W., Jr.: Refraction of the Rabbit's Eye in the Unexcited and Excited State, Am. J. Physiol. **127**:602, 1939. (*b*) Morgan, M. W., Jr., and Olmsted, J. M. D.: Response of the Human Lens to a Sudden, Startling Stimulus, Proc. Soc. Exper. Biol. & Med. **42**:612, 1939. (*c*) Morgan, M. W., Jr.; Olmsted, J. M. D., and Watrous, W. G.: Sympathetic Action in Accommodation for Far Vision, Am. J. Physiol. **128**:588, 1940. (*d*) Olmsted, J. M. D., and Morgan, M. W., Jr.: The Influence of the Cervical Sympathetic Nerve on the Lens of the Eye, ibid. **133**:720, 1941. (*e*) Mohney, J. B.; Morgan, M. W., Jr.; Olmsted, J. M. D., and Wagman, I. H.: The Pathway of Sympathetic Nerves to the Ciliary Muscles in the Eye, ibid. **135**:759, 1942.

4. Fincham, E. F.: A Study of Accommodation by Photography of the Living Lens and Ciliary Body in a Case of Aniridia, Tr. Ophth. Soc. U. Kingdom **40**:145, 1935.

and that on stimulation of the oculomotor nerve was about 10.00 D. In the great majority of these cats, therefore, the parasympathetic system was much more potent than the sympathetic in bringing about dioptric changes. In approximately 10 per cent of the cats, however, the reverse was true, the average being nearly 10.00 D. on stimulation of the sympathetic nerve and only 5.00 D. for parasympathetic stimulation.

It was noted in about 85 per cent of these cats that on stimulation of the cervical sympathetic nerve, whether it produced a relatively great or a relatively small change in dioptric power, the first and also the maximum change occurred in the horizontal meridian, thus giving rise to astigmatism of the direct ("with the rule") type, correctable by a convex cylinder with its axis at 90 degrees. In 1 cat the maximum was over 10.00 D. About 15 per cent of the cats did not show the phenomenon at all. It was present in the dogs and monkeys we examined, and for our whole series of animals the average value for astigmatism produced by stimulation of the cervical sympathetic nerve was slightly over 1.00 D.

It is conceivable that this astigmatism could be due either to a tilting of the lens about the 90 degree meridian or to a differential flattening of the cornea, lens or retina. If we assume that the refractive power of the lens in the cat is 20.00 D., as in man, then, using the formula cylinder $= F \tan^2 \Theta$, we shall find that in order to induce 1.00 D. of astigmatism the lens will have to rotate through an angle of some 12½ degrees. Our photographs [3d] of the lens profile gave no indication of rotation of the lens or of differential flattening of the cornea. Also, we found that the amount of astigmatism remained unchanged when all the extraocular muscles, including the retractor bulbi, were removed.[3c] Since this procedure does away with all possible distorting forces which could act on the globe of the eye, it seems most unlikely that there would be any differential flattening of the retina or cornea on sympathetic stimulation. This leaves only a differential flattening of the lens as the cause of the astigmatism.

In the cat there are two long ciliary nerves conveying sympathetic fibers into the eyeball, each of which divides into two. These four nerves surround the optic nerve and may be thought of as entering the eyeball at the four corners of a square. When each of the four nerves is stimulated individually, the axis of the induced astigmatism does not lie in the vertical meridian but tends to lean in a direction which can be described as "away from" the corner of the square at which the stimulated nerve is located. Furthermore, the skiascopic reflex is no longer regular, but its motion becomes what is commonly called "scissors motion."

The effects of sympathetic stimulation, viz. hypermetropia and astigmatism, are observable when an artificial pupil is used and the effects due to the dilatation of the pupil are eliminated.

The exact interpretation of these observations is still in the conjectural stage, but the most rational hypothesis is that the radial fibers of the ciliary muscle are innervated by the sympathetic nervous system; that these fibers on contraction increase the tension on the suspensory ligaments, thus flattening the lens,[5] and that their action is more effective in the horizontal meridian.

If one may assume that these observations on lower animals are applicable to human beings, a wide field for speculation is opened. For example, the action of the sympathetic system may be the cause of the change of axis of astigmatism

5. Hudelo, A.: Mécanisme de l'accommodation et myopie diabétique, Arch. d'opht. **47**: 70, 1930. Henderson, T.: The Anatomy and Physiology of Accommodation in Mammalia, Tr. Ophth. Soc. U. Kingdom **46**:280, 1926.

during active positive accommodation as reported by Hughes,[6] McDowell[7] and others. This theory also offers a logical explanation for the gradual increase in the incidence of indirect (against the rule) astigmatism with age greater than can be accounted for by the change in corneal curvature.

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6. Hughes, W. L.: Change of Axis of Astigmatism on Accommodation, Arch. Ophth. 26:742 (Nov.) 1941.

7. McDowell, G.: Why Does the Axis of the Astigmia Change? Optic. Developments, October 1932.

ANGIOMATOSIS RETINAE

REPORT OF SUCCESSFUL TREATMENT IN ONE CASE

PHILIP MERIWETHER LEWIS, M.D.
MEMPHIS, TENN.

Angiomatosis retinae is a relatively rare condition. Many experienced ophthalmologists have never seen it. Bedell [1] in 1931 found that less than 100 cases had been reported. Cordes and Hogan [2] in 1940 found that the number in the literature had risen to 135. Since that time about 10 additional cases have been reported.[3] The first description of the condition was in 1882 by Fuchs,[4] who considered it an arteriovenous aneurysm. Wood [5] in 1892 and Collins [6] in 1894 described the next cases. Von Hippel [7] was apparently the first to realize that the disease is a clinical entity, and since his publication in 1904 the condition has been called von Hippel's disease. In 1927 Lindau [8] reported that angiomatous tumors of the retina were often part of a general disorder characterized by angiomatous cysts of the cerebellum, medulla, spinal cord, adrenals, kidneys, liver, epididymis and ovaries. Thus Lindau's disease became established as an entity. His viewpoint has been adequately substantiated by other observers. He considered that in about 25 per cent of cases of retinal angiomatosis there are intracranial complications, principally angiomatous cysts of the cerebellum.

In this paper no effort will be made to review all the literature on the subject, as this has been adequately done by other writers.[9] A brief description of the disease will be given, with the report of a case in which treatment was carried out a year ago by diathermic punctures. It is hoped that this presentation will prove to be of some value to ophthalmologists who are not thoroughly familiar with this interesting disease.

OPHTHALMOSCOPIC FINDINGS

When an observer has once examined the eyegrounds in a typical case, or seen colored photographs of the fundus in the condition, recognition is fairly easy provided the characteristic appearance is present. However, the occurrence of bizarre types is not uncommon and may make the diagnosis difficult. Duke-Elder [10] stated that the usual clinical course may be divided into four stages: (1) the early stage, of vascular dilatation and formation of angioma; (2) the appearance of hemorrhages and exudates; (3) the stage of massive exudation and retinal detachment, and (4) the final stage of secondary glaucoma and destruction of the eye.

1. Bedell, A. J.: Am. J. Ophth. **14**:389, 1931.
2. Cordes, F. C., and Hogan, M. J.: Angiomatosis Retinae (Hippel's Disease), Arch. Ophth. **23**:253 (Feb.) 1940.
3. (*a*) Kaye, H.: Treatment of Angiomatosis Retinae, Arch. Ophth. **25**:443 (March) 1941. (*b*) Staz, L.: Brit. J. Ophth. **25**:167, 1941. (*c*) Craig, W. M.; Wagener, H. P., and Kernohan, J. W.: Lindau-von Hippel Disease, Arch. Neurol. & Psychiat. **46**:36 (July) 1941.
4. Fuchs, E.: Arch. f. Augenh. **11**:440, 1882.
5. Wood, D.: Tr. Ophth. Soc. U. Kingdom **12**:143, 1892.
6. Collins, E. T.: Tr. Ophth. Soc. U. Kingdom **14**:141, 1894.
7. von Hippel, E.: Arch. f. Ophth. **59**:83, 1904.
8. Lindau, A.: Acta ophth. **4**:193, 1927.
9. (*a*) Lloyd, R.: Am. J. Ophth. **11**:599, 1928. (*b*) Bedell.[1] (*c*) Cordes and Hogan.[2]
10. Duke-Elder, S.: Text-Book of Ophthalmology, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2849.

All observers seem to agree that the first sign is enlargement of a retinal vein, which rapidly becomes greatly dilated and tortuous. The accompanying artery also enlarges. Shortly thereafter a rounded, elevated, reddish or grayish mass is found far out in the periphery of the fundus, especially on the temporal side. As the enlargement of the vessels continues, it may become impossible to distinguish the artery from the vein. While the angioma and the vessels are increasing in size, retinal edema and exudative changes become manifest. A star-shaped figure may develop in the macula, or an appearance similar to that of circinate retinitis may be found. As Bedell [1] pointed out, the exudates, which at first consist of yellowish white flecks, by a process of coalescence become subretinal sheets. Retinal detachments may precede these exudative changes or may occur simultaneously. Eventually, complete retinal separation takes place, and, as Lloyd [9a] has shown, the diagnosis may be difficult unless an angiomatous mass and the enlarged vessels can be seen. Secondary glaucoma develops, and enucleation of the eye usually becomes necessary.

DIFFERENTIAL DIAGNOSIS

When retinal angiomatosis follows the usual pattern, the diagnosis is relatively easy, but the diagnosis of atypical or far advanced angiomatosis may be difficult. Confusion with glioma of the retina has often occurred. Another condition which at times simulates angiomatosis is Coat's diseases. Arteriovenous retinal aneurysm, choroidal tuberculosis, endophthalmitis and several other conditions, such as brain tumor and renal disease, may occasionally be mistaken for angiomatosis. Careful and repeated ophthalmoscopic examinations, transillumination and slit lamp studies, combined with a proper evaluation of the history and physical examination, will usually lead to a correct diagnosis.

PROGNOSIS

While in some cases the disease remains latent indefinitely, retinal angiomatosis is essentially a progressive disease. The prognosis, therefore, is definitely bad. Detachment of the retina or extensive exudation and hemorrhage lead to blindness, and secondary glaucoma leads to enucleation of the eyeball. Thus all patients who are seen at an early stage should be given the benefit of some form of treatment, because otherwise destruction of the eyeball is usually inevitable. If cerebellar symptoms are present the patient should be referred immediately to a competent neurosurgeon.

TREATMENT

Before local treatment is begun it is wise to have a thorough general and neurologic examination to determine whether the condition is simply von Hippel's disease or whether it is Lindau's disease. If it is Lindau's disease, the cerebellar tumor should be attacked first, and if this approach is successful, therapy of the eye should follow. Treatment may be attempted with roentgen rays or radium even in cases of advanced involvement, and, although vision may already have been destroyed, the use of radiation may prevent the necessity of enucleation.

In cases of early involvement various attempts have been made to destroy the growth. Applications of radium were employed by Holm,[11] Traquair,[12] Foster Moore [13] and others. Cordes and Hogan [2] reported definite improvement in 1 case

11. Holm, E.: Klin. Monatsbl. f. Augenh. **59**:319, 1917.
12. Traquair, H. M.: Tr. Ophth. Soc. U. Kingdom **53**:311, 1932.
13. Moore, R. F.: Tr. Ophth. Soc. U. Kingdom **55**:3, 1935.

in which they used high voltage roentgen therapy. Neame [14] used electrolysis in 1 case. Weve [15] used surface coagulation with diathermy and also diathermic punctures. It was the latter means which was employed in the case reported in this paper. It is particularly applicable in cases of a single angioma located far in the periphery. It is true that damage to the vision may be extensive, but it will not be much more than that caused in the operation for cure of retinal detachment. Furthermore, if the growth is not destroyed in some manner, it will destroy the eye. As a rule angiomas are located far in the periphery of the retina and are therefore readily accessible for treatment with diathermy. The ophthalmic surgeon may employ the same methods of localization of the growth as he is accustomed to use in localizing tears in cases of retinal detachment. The operative approach and technic are practically identical with those employed in the surgical cure of detachment of the retina by means of diathermy. Kaye [3a] has reported on 2 patients, a brother and a sister, whom Stallard treated, with apparently perfect results, by a combination of katholysis with surface and puncture diathermy.

TECHNIC

After localization of the angioma, that area of the sclera should be adequately exposed by a generous incision through the conjunctiva along the ora serrata. It will usually be necessary to draw aside a rectus muscle or divide the tendon and retract the muscle out of the field until the attack on the angioma has been completed. Surface coagulation may be employed over the area of the angioma and the surrounding retinal detachment. Scleral punctures with Walker micropins above and below the growth should be made and should be observed with the ophthalmoscope to check the localization of the angioma. The formation of a bubble, or what Walker [16] calls the "bubble vacuole," may be seen with the ophthalmoscope at the site of the puncture. Two or more punctures should be made just posterior to the angioma, either into or as near as possible to the enormously dilated vein and artery. After this, punctures directly into the angioma and the surrounding area of retinal detachment are made. The micropins should be inserted through the sclera about 2 mm. apart. From 30 to 50 milliamperes of current is used. The divided rectus muscle is carefully sutured back to its stump with no. 0000 chromic catgut. The conjunctiva is then closed with a running silk suture. The postoperative care of the patient is similar to that of patients with retinal detachment except that it need not be as strict or carried out for as long a period.

REPORT OF CASE

History.—W. K. B., a white man 25 years old, was seen in October 1941 because the vision of his left eye had been failing for the past six weeks. Recently he had had headaches after reading and also after working at his occupation as a cotton classer. There was no history of previous ocular troubles, headaches or dizziness.

The patient's history was without interest, as was that of his family. His father and mother were aged 57 and 52, respectively, and were in excellent health. The patient was an only child; he was married, but had no children. The parents' fundi were examined and found to be normal.

Ophthalmic Examination.—Both eyes were normal externally. Vision in the right eye was 20/25, corrected to 20/20 by a plus 0.50 D. cyl., axis 90. Vision in the left eye was 8/200, unimproved by lenses. The pupils were normal and dilated fully and evenly under homatropine cycloplegia. The media of each eye were clear, and the right fundus was normal.

14. Neame, H.: Am. J. Ophth. **20**:188, 1937.
15. Weve, H.: Tr. Ophth. Soc. U. Kingdom **59**:43, 1939.
16. Walker, C. B.: Am. J. Ophth. **17**:1, 1934.

The left fundus showed a most interesting picture. The disk was normal except for a marked dilatation of the inferior temporal vein. The accompanying artery was not enlarged until it reached a distance of 2 disk diameters from the papilla, where it enlarged rapidly, so that it became indistinguishable from the vein except by its course. The enlarged vessels led to a tumor mass almost 1 disk diameter in size, near the ora serrata in the 3:30 meridian. The mass was nearly round and was definitely elevated, with a smooth surface and grayish color. In and around the macular region were bright yellowish spots of "exudate," star shaped above the macula and in a large sheet below. The appearance of the exudate was somewhat similar to that in circinate retinitis.

Observations of the fundus were made several times in about three weeks, during which time consultations were held with Dr. E. C. Ellett and Dr. Ralph O. Rychener. It became apparent that the condition was a progressive one and that unless something was done the

Fig. 1.—Appearance of the fundus before operation.

eye would have to be enucleated. It was decided to try to destroy the growth and the dilated vessels by puncture diathermy. A careful physical examination revealed no abnormalities other than those of the eye.

Operation.—On November 11 the operation was performed with the help of Dr. Rychener. Preoperative sedation and local anesthesia were employed. The area was exposed as for a retinal detachment. The external rectus muscle was cut near its insertion and retracted to give an adequate exposure. The pupil had been widely dilated to permit easy ophthalmoscopic examination during the operation. One Walker micropin was placed just above and one just below the growth, a diathermy machine set to deliver 45 milliamperes of current being used. Micropins were then inserted posteriorly to the growth in an effort to strike or destroy the large feeding vessels. The vein was luckily transfixed with one pin, after which several were placed so as to thrombose both the vein and the artery. The "bubbles" produced by the punctures were observed with an ophthalmoscope to check the accuracy of the placements. After this, the entire area of the tumor and that of the surrounding retinal detachment were

studded with micropins. No hemorrhage occurred, so that ophthalmoscopic observation was possible throughout the operation. The external rectus muscle was reattached with fine chromic catgut and the conjunctiva closed with a running silk suture.

Postoperative Course.—The postoperative care was similar to that used after operation for retinal detachment. Both eyes were kept covered for seven days, after which pinhole glasses were used. The eye operated on was kept atropinized for about six weeks. The patient was allowed to resume his work four weeks after operation. Colored photographs of the fundus were taken twelve days after operation and have been taken at various intervals since that time. These were shown to demonstrate (1) the early changes, consisting of retinal edema and hemorrhages and thrombosis of the enlarged blood vessels, and (2) the progressive changes, which gradually led to the present condition of pigmented scar tissue. No enlarged vessels remain, but a few yellow spots persist in and around the macular region. No improvement in vision occurred after operation, but the destruction of the growth and the saving of the eyeball, with

Fig. 2.—Appearance of the fundus one year after operation.

a normal appearance and normal tension, constitute at least a partial victory. Had the patient been seen before the extensive degeneration of the macula had occurred, better function would probably have resulted. A year has passed, and no other angiomas and no cerebellar symptoms have developed.

SUMMARY AND CONCLUSIONS

1. Angiomas of the retina are discussed briefly regarding their symptoms, diagnosis, course, prognosis and treatment.

2. A rather simple method of treating these growths by puncture diathermy is described. It is especially applicable to simple angiomas which are discovered early.

3. A case in which treatment was by this method and follow-up lasted for one year was reported.

Dr. Rychener assisted in the management of this case.

MINERAL CONSTITUENTS OF SCLEROSED HUMAN LENSES

PETER W. SALIT, PH.D.
IOWA CITY

It has been well established that the distribution of the different mineral constituents of senile cataractous lenses differs considerably from that of normal lenses and that the changes become more and more marked with advance in the cataract.[1] Comparatively little study of a similar nature has been done with respect to sclerosis.[1c] The cataractous lenses in this study therefore were classified, according to a method published earlier,[2] into five stages of sclerosis: i. e., lenses with (1) no sclerosis (0), (2) slight sclerosis (+), (3) pronounced sclerosis (+ +), (4) very pronounced sclerosis (+ + +) and (5) highly advanced sclerosis (+ + + +).

In all, 72 lenses, extracted by the intracapsular method, were analyzed. The patients from whom the lenses were obtained varied in age from 44 to 87 years, with an average age of 69.1. The five groups of lenses consisted of 7, 10, 11, 25 and 19 lenses, respectively. The weights, on the basis of wet weight, for the first group (0) varied between 0.1905 and 0.2620 Gm. with an average of 0.2221 Gm. The respective ranges in weight for the four succeeding groups were 0.1647 to 0.2550 Gm. (+), 0.1790 to 0.2410 Gm. (+ +), 0.1500 to 0.2644 Gm. (+ + +) and 0.1017 to 0.2827 Gm. (+ + + +), with averages of 0.2200, 0.2026, 0.2037 and 0.1935 Gm., thus indicating a slight decrease in weight with advancing sclerosis. The water content of the lenses was ascertained by the difference in weight following drying to constant weight. The water content increased at a rather uniform rate from 67.6 per cent in practically normal lenses (0) to 75.4 per cent in lenses with highly advanced sclerosis (+ + + +).

Each group of lenses was ashed separately in a platinum dish in a muffle furnace at a temperature of approximately 560 C. After the ash was weighed it was dissolved in distilled water acidified with nitric acid and transferred by washing into a 50 cc. volumetric flask. The solution was made up to volume, and an aliquot amount was used in the determination of each of the following chemical constituents: potassium, sodium, calcium, phosphorus, chlorine and sulfur. The analyses were made according to the following methods: Salit's [3] colorimetric methods for potassium and sodium, Clark and Collip's [4] modification of Kramer-Tisdall's volumetric

From the Department of Ophthalmology, State University of Iowa College of Medicine.

1. (*a*) Burge, W. E.: Analyses of the Ash of the Normal and the Cataractous Lens, Arch. Ophth. **38**:435-450, 1909. (*b*) Mackay, G.; Stewart, C. P., and Robertson, J. D.: A Note on the Inorganic Constituents of Normal and Cataractous Human Crystalline Lenses, Brit. J. Ophth. **16**:193-201, 1932. (*c*) Salit, P. W.: Der Mineralbestand der kataraktösen und sklerosierten menschlichen Linsen, Arch. f. Ophth. **139**:654-667, 1938.

2. Salit, P. W.: Phospholipid Content of Cataractous and Sclerosed Human Lenses, Arch. Ophth. **16**:271-283 (Aug.) 1936; Water Content and Solids of Cataractous and Sclerosed Human Lenses, Am. J. Ophth. **21**:755-762, 1938.

3. Salit, P. W.: A New Triple Acetate Method for Sodium Determinations in Biological Materials, J. Biol. Chem. **96**:659-672, 1932; A Microcolorimetric Method for the Determination of Potassium in Biological Materials, ibid. **136**:191-200, 1940.

4. Clark, E. P., and Collip, J. B.: A Study of the Tisdall Method for the Determination of Blood Serum Calcium with a Suggested Modification, J. Biol. Chem. **63**:461-464, 1925.

method for calcium,[5] Whitehorn's [6] colorimetric method for phosphorus, Harvey's [7] volumetric method for chlorine and Salit's [8] modification of Rosenheim and Drummond's [9] volumetric method for sulfur.

The total amount of ash in terms of percentage varied from 0.889 in pronounced sclerosis (+ +) to 1.145 in practically normal lenses on the basis of wet weight, from 2.914 in pronounced sclerosis (+ +) to 3.821 in highly advanced sclerosis (+ + + +) on the basis of dry weight and from 1.280 in pronounced sclerosis (+ +) to 1.694 in practically normal lenses (0) on the basis of the water content. The total ash was therefore rather uniformly distributed between the different groups of lenses.

TABLE 1.—*Mineral Constituents of Sclerosed Human Lenses*

Stage of sclerosis	0	+	++	+++	++++
Number of lenses	7	10	11	25	19
Average weight of lenses, Gm.	0.2221	0.2200	0.2026	0.2037	0.1935
Water content, %	67.6	67.5	69.5	73.6	75.4
Average age of patients	64.7	65.8	59.7	74.2	70.8
Ash (%) on basis of					
Wet weight	1.145	0.977	0.889	0.991	0.907
Dry weight	3.533	3.006	2.914	3.407	3.821
Water content	1.694	1.450	1.280	1.491	1.386
K (%) on basis of					
Ash	14.82	16.60	13.07	10.22	3.52
Wet weight	0.170	0.162	0.116	0.101	0.070
Dry weight	0.524	0.500	0.381	0.348	0.270
Water content	0.251	0.241	0.167	0.143	0.095
Na (%) on basis of					
Ash	7.91	9.32	16.71	17.79	26.54
Wet weight	0.091	0.092	0.148	0.177	0.263
Dry weight	0.280	0.283	0.486	0.605	1.010
Water content	0.134	0.137	0.213	0.249	0.357
Ca (%) on basis of					
Ash	0.453	1.067	1.222	1.525	2.652
Wet weight	0.005	0.010	0.011	0.015	0.026
Dry weight	0.016	0.031	0.036	0.052	0.101
Water content	0.008	0.015	0.016	0.021	0.026
PO_4 (%) on basis of					
Ash	10.34	9.09	10.00	4.76	4.17
Wet weight	0.118	0.089	0.089	0.048	0.042
Dry weight	0.363	0.273	0.292	0.163	0.158
Water content	0.139	0.132	0.128	0.067	0.056
Cl (%) on basis of					
Ash	2.06	2.27	11.72	2.18	18.06
Wet weight	0.024	0.022	0.104	0.022	0.179
Dry weight	0.073	0.068	0.341	0.074	0.687
Water content	0.035	0.033	0.150	0.030	0.243
SO_4 (%) on basis of					
Ash	0.54	6.19	4.49	7.63	3.12
Wet weight	0.006	0.061	0.038	0.077	0.030
Dry weight	0.019	0.187	0.142	0.260	0.113
Water content	0.010	0.089	0.061	0.107	0.040

The potassium content was nearly the same in practically normal (0) and in slightly sclerosed lenses (+), amounting to 14.82 and 16.60 per cent, respectively, on the basis of ash. It decreased to 13.07, 10.22 and 3.52 per cent, respectively, in the succeeding stages of sclerosis (+ +, + + +, + + + +). On the basis

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6. Whitehorn, J. C.: A Method for the Determination of Lipoid Phosphorus in Blood and Plasma, J. Biol. Chem. **62**:133-138, 1924.

7. Harvey, S. C.: The Quantitative Determination of the Chlorids in the Urine, Arch. Int. Med. **6**:12-18 (July) 1910.

8. Salit, P. W.: A Note on the Rosenheim-Drummond Benzidine Method for Sulfur, to be published.

9. Rosenheim, O., and Drummond, J. C.: A Volumetric Method for the Estimation of Ethereal and Inorganic Sulphate in Urine, Biochem. J. **8**:143-151, 1914.

of wet weight it decreased uniformly through all stages from 0.170 per cent in practically normal lenses (0) to 0.070 per cent in highly advanced sclerosis (++++). Correspondingly it decreased on the basis of dry weight and the water content from 0.524 to 0.270 per cent and from 0.251 to 0.095 per cent, respectively.

There was little change in the phosphorus content up to the stage of pronounced sclerosis, the phosphorus values in terms of phosphate being 10.34, 9.09 and 10.00 per cent for practically normal lenses (0), slight sclerosis (+) and pronounced sclerosis (++), respectively. Then there was a sudden decrease to 4.76 and 4.17 per cent for the last two stages of sclerosis (+++ and ++++). On the basis of wet weight, dry weight and the water content the values decreased with each stage of advancing sclerosis with great uniformity; they decreased from 0.118, 0.363 and 0.139 per cent in practically normal lenses to 0.042, 0.158 and 0.056 per cent, respectively, in lenses with highly advanced sclerosis.

TABLE 2.—*The Sum Totals of Cations (K^+, Na^{++}, Ca^{++}) in Different Stages of Sclerosis*

Stage of sclerosis	0	+	++	+++	++++
Percentage on basis of					
Ash	23.180	26.980	31.000	29.540	32.720
Wet weight	0.258	0.264	0.275	0.298	0.359
Dry weight	0.820	0.814	0.903	1.005	1.380
Water content	0.393	0.393	0.396	0.413	0.488

TABLE 3.—*The Sum Totals of Anions (PO_4^{---}, Cl^-, SO_4^{--}) in Different Stages of Sclerosis*

Stage of sclerosis	0	+	++	+++	++++
Percentage on basis of					
Ash	12.940	17.550	26.200	14.570	25.360
Wet weight	0.148	0.172	0.231	0.147	0.251
Dry weight	0.455	0.528	0.775	0.497	0.958
Water content	0.183	0.254	0.339	0.204	0.339

TABLE 4.—*The Sum Totals of Cations and Anions (K^+, Na^+, Ca^{++}, PO_4^{---}, Cl^-, SO_4^{--}) in Different Stages of Sclerosis*

Stage of sclerosis	0	+	++	+++	++++
Percentage on basis of					
Ash	36.130	44.530	57.200	44.100	58.070
Wet weight	0.406	0.436	0.506	0.440	0.610
Dry weight	1.275	1.342	1.678	1.502	2.338
Water content	0.576	0.647	0.735	0.617	0.827

On the other hand, on the basis of ash sodium increased with great regularity through all the stages of sclerosis from 7.913 per cent in practically normal lenses to 26.540 per cent in highly advanced sclerosis. On the basis of wet weight, dry weight and water content the values increased from 0.091, 0.280 and 0.134 per cent in practically normal lenses to 0.263, 1.009 and 0.357 per cent, respectively.

Similarly, calcium increased from 0.453 per cent in practically normal lenses to 2.652 per cent in highly advanced sclerosis on the basis of ash, from 0.005 to 0.026 per cent on the basis of wet weight, from 0.016 to 0.101 per cent on the basis of dry weight and from 0.008 to 0.036 per cent on the basis of the water content.

There is a strong indication that chlorine likewise increases with advancing sclerosis, but with less regularity than sodium and calcium. It increased from 2.06 per cent in practically normal lenses to 2.27 per cent in slightly sclerosed lenses and to 11.72 per cent in lenses with pronounced sclerosis on the basis of ash. It had a low value of 2.18 per cent in very pronounced sclerosis (+++) but a high

value of 18.06 per cent in highly advanced sclerosis (+ + + +). Corresponding increases and irregularities were shown when the values were computed on the basis of wet weight, dry weight and the water content. It was felt that the irregularities were due to loss of some chlorine in the process of ashing, especially in the case of lenses with very pronounced sclerosis (+ + +). But the irregularities were not pronounced enough to indicate that the two high values (11.72 and 18.06 per cent) in pronounced and highly advanced sclerosis were due merely to coincidence.

Still greater irregularities occurred in the sulfur content of the different groups of lenses, which must also be attributed to some loss of sulfur in the ashing process. But again, on the whole there was some indication of a slight increase in this constituent with advancing sclerosis. On the basis of ash the lowest value, 0.542 per cent, in terms of sulfate was shown by practically normal lenses (0) and the highest value, 7.63 per cent, by the group with very pronounced sclerosis. The results are in agreement with those of Mackay and associates, who found slightly more sulfur in cataractous than in normal lenses.

When the sum totals of all the cations for which the lenses were analyzed (K^+, Na^+, Ca^{++}) were computed for the five groups of lenses, their differences were found to be a great deal less pronounced than those between the individual constituents. But, on the whole, there was a gradual increase in the values with advancing sclerosis; they increased from 23.18 per cent in practically normal lenses to 26.98, 31.00, 29.54 and 32.72 per cent in the succeeding more advanced stages of sclerosis on the basis of ash. Similarly, the sum totals of anions (PO_4^{---}, Cl^-, SO_4^{--}) incraesed from 12.94 to 17.55, 26.20, 14.57 and 25.36 per cent, respectively. Accordingly, the sum totals of all the electrolytes (cations plus anions) for which the lenses were analyzed increased with advancing sclerosis, i. e., from 36.13 per cent in practically normal lenses to 44.53, 57.20, 44.10 and 58.07 per cent in the succeeding more advanced stages of sclerosis. This, however, accounts for less than half of the total ash. All ash, of course, contains a great deal of carbonate, and its presence was indicated by the effervescence test on the addition of an acid. Therefore, the largest part of the undetermined ingredients of the ash must have been made up of carbonates.

SUMMARY

In all, 72 sclerosed human lenses, extracted by the intracapsular method, were analyzed for their water content and mineral constituents.

The ages of the patients varied between 44 and 87 years, with an average of 69.1. The lenses were classified into the following five groups according to stage of sclerosis: practically normal, slightly sclerosed, with pronounced sclerosis, with very pronounced sclerosis and with highly advanced sclerosis.

The average weight of the lens decreased at a rather uniform rate from 0.2221 Gm. for practically normal lenses to 0.1935 Gm. in highly advanced sclerosis. The water content, on the other hand, increased from 67.6 to 75.4 per cent, respectively. Potassium and phosphorus (PO_4), computed on the basis of the total ash, decreased, respectively, from 14.82 and 10.34 per cent in practically normal lenses to 3.52 and 4.17 per cent in highly advanced sclerosis. On the other hand, sodium, calcium and chlorine, also computed on the basis of the ash, increased from 7.91, 0.45 and 2.06 per cent in practically normal lenses to 26.54, 2.65 and 18.06 per cent, respectively. There is an indication, in spite of certain irregularities, that the sulfur content also increases somewhat with advancing sclerosis.

University Hospitals, State University of Iowa.

PARADOXIC ESOTROPIA DURING CYCLOPLEGIA

CAPTAIN H. SAUL SUGAR
MEDICAL CORPS, ARMY OF THE UNITED STATES

The disappearance or diminution in degree of accommodative esotropia during cycloplegia is frequently encountered and is explained on the basis of the Donders theory of accommodation-convergence association. The appearance of, or an increase in, esotropia during cycloplegia has hitherto not been reported. Four cases of this paradoxic esotropia are therefore being reported, together with a probable explanation of the phenomenon.

REPORT OF CASES

CASE 1.—Lieutenant A. N. D., aged 33, had visual acuity in the right eye of 20/70, with ability to read Jaeger type 7, corrected to 20/30, Jaeger type 2, and in the left eye of 20/20, with ability to read Jaeger type 2, corrected to 20/20, Jaeger type 1. The patient was first seen on Jan. 13, 1942, at which time a right exotropia, varying from 8 to 20 prism diopters for 20 feet (610 cm.) and 2 to 34 prism diopters for 15 inches (38 cm.) was measured with loose prisms and the cover test. No incomitance was noted. The near point of convergence

Fig. 1 (case 2).—The patient before and during cycloplegia.

was 20 mm. During cycloplegia induced with 2 drops of 5 per cent homatropine hydrobromide solution the necessary refractive correction was found to be + 0.25 D. sph. ⌒ + 1.00 D. cyl., axis 90, for the right eye and + 0.50 D. sph. ⌒ + 1.00 D. cyl., axis 90, for the left. A rather constant right esotropia measuring 14 prism diopters for 20 feet and 45 prism diopters for 15 inches was found. On disappearance of the cycloplegia the eyes resumed their original exotropic state. Reexamination of the patient subsequently revealed the same phenomenon during cycloplegia. A 5 mm. recession of the right external rectus muscle was done on March 5 and a similar recession of the left external rectus muscle on April 10, with resulting parallelism. Cycloplegia caused temporary reappearance of the esotropia.

CASE 2.—Private J. E. K., aged 20, had visual acuity in the right eye of 20/50, with ability to read Jaeger type 4, not correctible, and in the left eye of 20/20, with ability to read Jaeger type 1. In 1938 an operative procedure had been done on the horizontal rectus muscles of each eye to correct a right esotropia. The patient was examined on Nov. 6, 1942 and found to have a concomitant right esotropia of 2 prism diopters for 20 feet and 8 prism diopters for 15 inches. The near point of convergence was at the bridge of the nose. During cycloplegia induced with 5 per cent homatropine hydrobromide solution the refractive error was found to be 0.50 D. of hyperopia for the right eye and 0.75 D. for the left. A paradoxic increase in esotropia measuring 42 prism diopters for 20 feet and 48 prism diopters for 15 inches was present, the esotropia decreasing to the original amount when the cycloplegia wore off (fig. 1). Repeated cycloplegia resulted in a recurrence of the phenomenon.

From the Eye Clinic of the Barnes General Hospital, Vancouver, Wash.

CASE 3.—Private A. L., aged 28, had visual acuity in the right eye of 20/300, with inability to read Jaeger print, not correctible, and in the left eye of 20/15, with ability to read Jaeger type 1. The patient gave a history of having had right esotropia since birth. He was examined on Nov. 28, 1942 and found to have concomitant right esotropia of 8 prism diopters for 20 feet and 16 prism diopters for 15 inches. A persistent hyaloid artery was present in the right eye. The near point of convergence was 25 mm. During cycloplegia induced with 5 per cent homatropine hydrobromide solution the necessary refractive correction was found to be -1.50 D. sph. $\bigcirc$ $+$ 1.25 D. cyl., axis 135, for the right eye and $+$ 0.75 D. sph. for the left. A paradoxic increase in esotropia measuring 38 prism diopters for 20 feet and for 15 inches was present. The esotropia decreased to its original amount after the cycloplegia wore off. Repeated cycloplegia resulted in a recurrence of the phenomenon. Operation on the horizontal rectus muscles resulted in parallelism.

CASE 4.—Private A. D. S., aged 28, had visual acuity in the right eye of 20/15, with ability to read Jaeger type 1, and in the left eye of 20/50, with ability to read Jaeger type 7, corrected to 20/25, Jaeger type 2. The left external rectus muscle was shortened in 1926 because of left convergent strabismus, which had begun at the age of 6, following an attack of influenza. The eyes were parallel for distant and for near vision in the cover test. Macular suppression in the left eye was present. The near point of convergence was 30 mm. During cycloplegia induced with 5 per cent homatropine hydrobromide solution the necessary refractive correction was found to be $+$ 2.25 D. sph. $\bigcirc$ $+$ 0.25 D. cyl., axis 90, for the right eye and $+$ 3.00 D. sph. $\bigcirc$ $+$ 0.37 D. cyl., axis 90, for the left. A paradoxic esotropia measuring 23 prism diopters for distant and for near vision was present (fig. 2). The eyes returned to parallelism when the cycloplegia wore off. Repeated cycloplegia resulted in a recurrence of the phenomenon.

Fig. 2 (case 4).—The patient before and during cycloplegia.

COMMENT

The dominant eye was hyperopic in each case. The cycloplegic corrections for the dominant eye were $+$ 0.50 D. sph. $\bigcirc$ $+$ 1.00 D. cyl., axis 90, in case 1; $+$ 0.75 D. sph. in cases 2 and 3, and $+$ 2.25 D. sph. $\bigcirc$ $+$ 0.25 D. cyl., axis 90 in case 4. Some degree of amblyopia and definite suppression were present in the other eye in each case. The paradoxic esotropia during cycloplegia always involved the amblyopic eye.

The original angular relationship between the two eyes was apparently not a factor in the occurrence of the paradoxic esotropia, since without cycloplegia, there was no deviation in 1 case and the strabismus was divergent in 1 and slightly convergent in 2.

An explanation for the phenomenon was found during observation of the second case (that of J. E. K.). This was based on the belief that during cycloplegia the blurring of vision led to attempts to clear the blur by accommodation. Such "voluntary" accommodation stimulates an associated convergence, leading to an actual esotropia. Patient J. E. K. during cycloplegia was asked to fix his gaze on the 20/20 letters at 20 feet. A pinhole disk was then placed before his better eye so that he could obtain clear vision by using only the nonrefracted axial rays

of light. The eyes then resumed their original state of near parallelism. When the pinhole disk was removed the esotropia reappeared. The same result was obtained by placing the full cycloplegic correction before the better eye. These tests were applied in the last 2 cases with the same results. The disk or correcting lenses did not affect the esotropia when placed before the amblyopic eye.

This phenomenon appears to substantiate the presence of two types of accommodation-convergence relationship, the involuntary (occipital) and the "voluntary" (frontal). As discussed by Chavasse,[1] accommodation and convergence may function independently at the occipital level, but at the frontal, or "voluntary," level they are always associated, at least in prepresbyopes. It is on the frontal level that both paradoxic esotropia and accommodative esotropia are dependent.

In cases of excessive hyperopia the occipital accommodative control is insufficient to satisfy the accommodative need; so it is supplemented by the frontal mechanism, which, being firmly associated with convergence, may result in accommodative esotropia. This is relieved early in the course, when it is uncomplicated, by the use of convex lenses or by the use of a cycloplegic. In these instances the blurring under cycloplegia is possibly too great for an attempt to stimulate the frontal "voluntary" accommodation-convergence mechanism.

With low degrees of hyperopia, the frontal mechanism is called into play only during cycloplegia in order to clear up blurred vision. In a person with normal binocular vision any tendency to convergence is inhibited by the diplopia which would result. In a person with monocular suppression there is no diplopia; consequently a paradoxic esotropia may result. When the vision of the dominant eye is cleared with correcting lenses or a pinhole disk, the need for accommodation is relieved, and the eyes return to their original position.

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1. Chavasse, F. B., in Worth, C.: Worth's Squint, revised by F. B. Chavasse, ed. 7, Philadelphia, B. Blakiston's Son & Co., 1939.

Clinical Notes

SIMPLEST INSTRUMENT FOR REMOVAL OF FOREIGN BODIES FROM CORNEA

MAJOR ALFRED APPELBAUM,
MEDICAL CORPS, ARMY OF THE UNITED STATES

While on a vacation several years ago, I was called on to remove a foreign body deeply embedded in the cornea. No instruments were available. The procedure was attempted with an ordinary hypodermic needle attached to an insulin syringe as a handle. The experience convinced me that in the simple "needle" one has an instrument which surpasses any other for executing this common, but nevertheless seriously important, task.

After persevering with several varieties and sizes, I found that the Luer-Lok type stainless steel 19 gage 2½ inch (62 cm.) needle with a long bevel served the purpose best. The cannula is of sufficient length for convenient manipulation. It requires no handle and constitutes a complete instrument in itself.

For the past four years I have used nothing but one of these needles when removing a foreign body from the cornea and, with unabated enthusiasm, continue to do so. The more spectacular and more expensive combination of hypodermic needle and special handle recently described by Harding[1] certainly offers no advantages.

Sterilization is accomplished by boiling only when the one needle is used again and again and infrequently. Where foreign bodies are common, sterilization is best accomplished in the autoclave. The unsterile, dry, clean needle is placed point down in a small test tube, culture tube or vial containing a pledget of absorbent cotton at the bottom to protect the point. Another pledget of absorbent cotton serves as a stopper. A number of such units, depending on requirements, are placed in an ointment jar or dressing jar of appropriate size, ready for the autoclave. At the close of the day, used needles are cleansed with a piece of gauze, replaced in their containers, resterilized and returned to the jar. When necessary, the points may be ground down on a stone.

The operator holds the hub of the needle between the thumb and the index finger, steadying the cannula with the middle finger in such a way that the bevel faces him. With a technic similar to that employed when the conventional instruments are used, removal of the average embedded corneal foreign body becomes an operation timed in seconds. Frequently one can even remove a rust ring with ease by simply guiding the point of the needle under the outer circumference of the ring and through the hole of the ring. The cornea invariably suffers a minimum of trauma, often an amount so negligible that the instillation of an antiseptic ointment into the conjunctival sac can supplant the usual eye dressing. A competent operator need not fear the possibility of perforation of the cornea.

I have found the needle described an efficient, practical, inexpensive, readily available, time-saving instrument, both in civilian practice and during my service at the Station Hospital, Camp Kilmer, N. J., where corneal foreign bodies were numerous. It should be equally useful in the first aid room of the industrial plant, in the ophthalmic clinic and in the field hospital, where a sufficient number of needles may be kept on the dressing table ready for instant application.

111 East Sixty-First Street, New York.

1. Harding, G. F.: Instrument for Removal of Foreign Body from Cornea, Arch. Ophth. **29**:134 (Jan.) 1943.

PORTABLE SLIT LAMP AND ITS CLINICAL VALUE

MAJOR EMANUEL KRIMSKY, MEDICAL CORPS, ARMY OF THE UNITED STATES

The hand slit lamp is especially suitable for the bedside, the home or the clinic, where the large slit lamp may not be readily available. For the child or the restless adult patient the hand slit lamp proves indispensable. Even in the busy clinic, where time limits the examiner to selecting only a few patients for detailed slit lamp biomicroscopy with the large instrument, the hand slit lamp is helpful in conjunction with the hand ophthalmoscope in the detection and study of pathologic changes in the cornea, iris and lens. Its value, therefore, lies not necessarily in providing the basis of a conclusive diagnosis of more obscure lesions but in providing a flexible aid in the diagnosis of more superficial pathologic changes, as well as a means of rapid and satisfactory inspection of minute foreign bodies.

In 1932 I [1] described an illuminated loupe, stating:

> One of the difficulties confronting the ophthalmologist in the use of the monocular loupe is in obtaining a sufficient amount of condensed light at a suitable focal distance. Besides the fact that one hand is occupied in holding the condensing lens, the source of the illumination may not always be close or conveniently at hand. In order to overcome these shortcomings

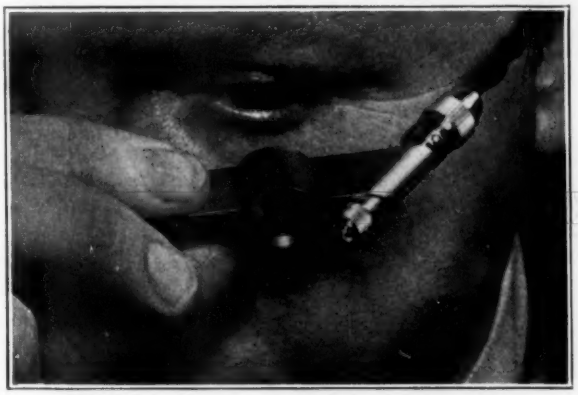

Fig. 1.—The hand unit.

> it occurred to me that if the light source and condenser could be combined as a unit and this in turn attached or fastened to the loupe, a satisfactory and reliable source of illumination might be effected to assist the operator in his observations.

I also described how this crude model could be used as a hand slit lamp.

In designing a slit lamp for hand use, the problem was to provide a so-called featherweight instrument [2] that could be carried in the hand and would not interfere with the free use of the ophthalmoscope. Hence, besides being a light instrument, it had to be an independent unit, as the use of a common battery handle for the two instruments might prove time consuming and expose them to breakage through frequent interchange. I have, therefore, found it practical to respect the intactness of the ophthalmoscope with its battery handle and to supply the slit lamp with a separate medium-sized battery handle (carried in the coat pocket), using no. 935 batteries connected to the slit lamp by means of a fine silk-woven wire. Such an arrangement permits the slit lamp to be slipped back into the coat pocket, adds to its lightness by not being joined directly to the handle, obviates frequent disturbance of the ophthalmoscope, is time saving and permits the instrument to be held between two fingers instead of by two hands (fig. 1). The unit may also be operated from

1. Krimsky, E.: A Modified Monocular Loupe, Arch. Ophth. **8**:272-274 (Aug.) 1932.
2. Krimsky, E.: A Featherweight Slit-Lamp, Arch. Ophth. **21**:1033-1035 (June) 1939.

a current controller connected to the house current. Furthermore, as will be shown later, an extra unit with a spring clamp attachment to the wearer's eyeglass or frame permits the free use of both hands by the operator.

This new slit lamp, like its forerunners, has been designed to include the following features: (1) centralization and proper angulation of light at an angle of 45 degrees, (2) firmness, (3) lightness, (4) compactness and simplicity of

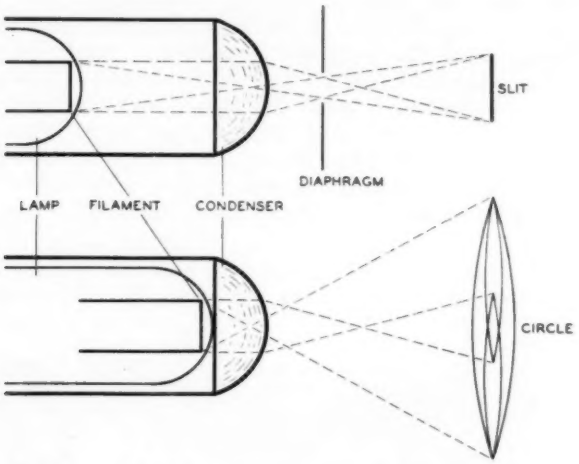

Fig. 2.—Optical basis of the portable slit lamp.

Fig. 3.—Slip-over attachment for examiner's eyeglasses.

operation and (5) proper quality and quantity of illumination. The new features are (1) an automatic device to change the beam progressively from a vertical slit to a transverse slit and finally to a homogeneous circle of light, (2) an attachment to permit the instrument to be worn over an eyeglass or frame, (3) a square lamp filament and (4) a pinhole cap to exclude extraneous rays.

The lamp unit consists of a light carrier, a straight filament bulb and a hemispherical condenser. This unit has been made to provide automatically and

progressively a vertical slit, a horizontal slit and a homogeneous circle of light by the simple turning of the base of the unit, which has had incorporated in it a helical mount, which operates in such a way as to slide the bulb backward or forward without displacing the condenser. By such manipulation, the approximation of bulb and condenser produces a circle of light, and separation leads to a slit light by bringing the filament in the focal plane of the condenser. The slit beam is comparable to that obtained with the straight filament lamp, as in the hand ophthalmoscope. However, a truer slit has been made possible by means of a square filament (designed by me) instead of the arch-shaped filament and by the incorporation of a pinhole cap ($\frac{1}{16}$ inch [0.16 cm.] opening) which fits over the condenser lens cap (fig. 2).

The eyeglass slip-over attachment (fig. 3) is also provided with a channel to permit the insertion of a common light carrier like that for the hand unit. This attachment has a longer focus lens of 4 power magnification, which is less satisfactory for critical investigation but more desirable for minor operative procedures, such as the removal of a foreign body or corneoscleral sutures or epilation of eyelashes. Not only does the slit lamp make it easily possible to bring a foreign body into proper relief, but the fixed attachment on the eyeglass or frame enables the operator to control the patient better through fixation of the lids with one hand and surgical manipulation with the other.

POSSIBLE DANGER IN USE OF MERTHIOLATE OPHTHALMIC OINTMENT

FRANCIS A. ELLIS, M.D., BALTIMORE

When the recent article on merthiolate dermatitis by Ellis and Robinson [1] was presented before the Dermatological Section of the Baltimore City Medical Society, the possibility of a severe ocular complication resulting from the use of merthiolate ophthalmic ointment was discussed. At that time there were no reports of contact dermatitis or of positive results of patch tests with this ointment, nor had proof been presented that merthiolate could cause by contact an inflammation of the mucous membrane. It was the opinion of several discussers that the question of ocular complications should be dismissed until experimental proof of a deleterious effect could be obtained. If merthiolate ophthalmic ointment could cause in a merthiolate-sensitive patient a severe reaction on the conjunctiva and cornea comparable to the cutaneous injury reported by Ellis and Robinson, then the use of this ointment on the sensitive patient would be dangerous and perhaps produce keratitis and ulceration of the cornea with subsequent impairment of vision.

REPORT OF CASES

CASE 1.—On February 21 the patient in case 1 of the previous report [1] presented himself for examination. One week previously tincture of merthiolate had been applied to the anterior third of his left foot. Since his previous disability due to merthiolate the patient had changed his place of employment, and an uninformed first aid attendant was unaware of his sensitiveness to the antiseptic. On the anterior third of the left foot, the site where the tincture of merthiolate had been applied, there developed within twelve hours an acute vesicular dermatitis. Two days later there appeared in the treated area superficial confluent erosions covered by seropurulent crusts. Treatment consisted of application of 2 per cent aqueous solution of gentian

1. Ellis, F. A., and Robinson, H. M., Jr.: Cutaneous Sensitivity to Merthiolate and Other Mercurial Compounds, Arch. Dermat. & Syph. **46**:425 (Sept.) 1942.

violet, use of compresses soaked in 1:32 solution of aluminum acetate and application of 5 per cent sulfathiazole (2-[paraaminobenzenesulfonamido]-thiazole) in a base containing 90 per cent petrolatum and 10 per cent glycerol monostearate. The lesion healed in two weeks. On the flexor surface of the forearm an area 0.5 cm. in diameter was painted with tincture of merthiolate, and a patch test with 1:5,000 merthiolate ophthalmic ointment was carried out. Within twenty-four hours both tests resulted in 3 plus reactions. An area on the mucous membrane of the right cheek was wiped dry, and tincture of merthiolate was applied. This caused within forty-eight hours an area of stomatitis consisting of a livid erythema with superficial erosions on an edematous base. An occupational dermatitis developed twice owing to treatment applied in the first aid room.

CASE 2.—H. M., a white man aged 44, for many years had tolerated the use of tincture of merthiolate as a local antiseptic. In April 1942 he had applied various ointments and tincture of merthiolate to an abrasion on the flexor surface of the right forearm. Eight days before he was examined a severe, acute, vesicular, erythematous dermatitis measuring approximately 8 by 12 cm. developed in and around the treated area. The results of patch tests with the various medicinal agents used locally by the patient were negative except in the case of tincture of merthiolate, which caused a strongly positive reaction. A patch test with merthiolate ophthalmic ointment caused a 3 plus reaction. An incapacitating dermatitis developed on the arms, forearms and face. Three weeks after the patient was first seen the dermatitis was moderately active. A 1 cm. area on the inner surface of the cheek was painted with tincture of merthiolate, and in forty-eight hours this area was edematous and was covered by many erythematous, edematous papules and vesicles approximately 2 mm. in diameter.

Five months later, in September 1942, a drop of 1:1,000 thiosalicylic acid in 95 per cent ethyl alcohol delivered from a glass rod 3 mm. in diameter was applied without dressing to the flexor surface of the left arm. Within twenty-four hours an erythematous dermatitis developed. One week later the area of the patch test showed a 2 cm. erythematous, well defined plaque covered by a mild scale with slight evidence of vesiculation. There was also a mild erythematous and slightly vesicular dermatitis at the site of the eruption caused by tincture of merthiolate five months previously. The test suggested that the thiosalicylic acid is the sensitizing radical in sodium ethylmercurithiosalicylate (merthiolate) dermatitis.

COMMENT

The positive results of patch tests demonstrated that the 2 patients who were sensitive to tincture of merthiolate were also sensitive to 1:5,000 merthiolate ophthalmic ointment and that merthiolate is capable of causing an inflammation of the mucous membrane in patients who are sensitive to the drug.

In view of these facts it is recommended:

1. That merthiolate ophthalmic ointment should not be used in or about the eye unless it has been previously demonstrated by patch tests that the patient is not sensitive to the ointment.

2. That the package should be labeled to warn the consumer that such tests should be made previous to the use of merthiolate ophthalmic ointment in or about the eye.

Since a patient may become sensitized to merthiolate while using the ophthalmic ointment, it may be advisable to withdraw this product from the market before a case of permanent ocular damage occurs, in spite of the fact that no cases of ocular injury due to merthiolate ointment have been reported.

8 East Madison Street.

Ophthalmologic Reviews

EDITED BY DR. FRANCIS HEED ADLER

NIGHT VISION

WILLIAM JOHN HOLMES, M.D.
HONOLULU, TERRITORY OF HAWAII

The purpose of this paper is to review the subject of night vision and to present the cardinal principles which govern man's ability to perceive light and discriminate detail in the dark. The bulk of the literature on lighting and on the effect of light on the eye deals with conditions which exist at optimal intensities of illumination, at which maximal ease of seeing is provided. Relatively little attention has been paid to ocular function at minimal intensities of illumination, at which seeing is barely sustained, such as prevail under black-out lighting conditions. The intelligent coordination of lighting principles with fundamental ophthalmologic concepts is of importance in wartime, especially in localities where black-outs or dim-outs are a military necessity.

PHYSIOLOGIC CONSIDERATIONS

The ability of the eye to function at low brightnesses depends on the integrity of the retinal rods and is called scotopic vision. Subjectively the sensation that accompanies this phenomenon is devoid of color or only slightly tinged with the colors of the shorter wave end of the visible spectrum (bluish and violet). For distinct seeing in bright lights the term photopic vision is used. This is mediated by the retinal cones, which transmit the long wave end of the visible spectrum and also serve for the discrimination of colors. The cones are most abundant in the central portion of the retina, while the rods predominate in the periphery. In dim light, the area in the visual field corresponding to the fovea is relatively blind in contrast to the peripheral portions because the majority of the cones possess thresholds which are higher than those of the rods.

Scotopic seeing is somewhat analogous to the visual processes which take place in the eye of a patient afflicted with total congenital color blindness. A person with such a defect is not able to perceive colors; he sees only black and white. His visual acuity is greatly diminished. He is dazzled by light and exhibits nystagmus. His dark adaptation is normal, and his light adaptation is diminished. It is supposed that in the eyes of such persons only the rods function and the cones are abnormal or absent. The reduction of central vision is due to the relative central scotoma, the nystagmus is explained by the loss of central fixation and the dazzling is a consequence of the deficient light adaptation.

According to the von Kries [1] theory, which is fairly universally accepted, the normal human retina consists of two separate components: a day-seeing part, noted typically at the fovea, and a night-seeing portion, functioning at the periphery.

At the moment when rod vision changes into cone vision the light intensity varies between 300 to 500 milli-foot-lamberts.[2] Otuka,[3] using the meter candle as the unit of measurement, reported that the change takes place between 0.054

1. von Kries, J.: Ueber die absolute Empfindlichkeit der verschiedenen Netzhautteile im dunkel-adaptierten Auge, Ztschr. f. Psychol. u. Physiol. d. Sinnesorg. **15**:327, 1897.

2. The figures quoted represent ocular, and not retinal, visibility curves. To obtain the latter, absorption by the ocular media has to be accounted for. According to Ludvigh and

(Footnotes continued on next page)

to 0.011 lux in the light and between 0.074 to 0.145 lux in the dark. For practical considerations Hecht [4] suggested that full moonlight serve as an arbitrary dividing line between rod and cone vision.

The eye is able to adapt itself to extremes of illumination ranging from summer sunlight to faint starlight, a scale of about 100,000,000 to 1. The immediate effect of an abrupt change from light to darkness is a reduction of the visual acuity. Coincident with the drop in central vision, an increase in the light sensibility of the peripheral portion of the retina takes place. The increased capability of the eye to obtain clear vision when exposed to darkness is known as dark adaptation. The process begins immediately when the subject enters the dark and rapidly increases for the first ten minutes. Subsequently a more gradual increase in sensitivity takes place and at the end of forty minutes dark adaptation is practically complete. The dark-adapted retina has the ability to perceive light in decreasing degrees of illumination down to 0.00001 foot lambert [5] and maintains it for at least six hours and possibly longer.

The effectiveness of the visual processes in dim light are determined by the visibility of the object and by the ocular, systemic and psychologic state of the observer.

VISIBILITY OF THE OBJECT

Factors which affect the visibility of the object are its size, its brightness and color, the contrast it forms with the surroundings and the duration of the stimulus on the retina.[6] Brightness and color are responsible for the perception of an object, while contrast figures in the discrimination of detail of the pattern. When the contrast between an object and its background is reduced, visibility will correspondingly be reduced. When the size of the object viewed is increased, the role played by contrast in recognition of its details is similarly increased. Over a wide range of intensities the eye is able to perceive differences in brightness not as absolute values of the two intensities but as differences which depend on their ratio. This ratio is expressed by Weber-Fechner's law, which states that the visual brightness is proportional to the logarithm of the stimulus intensity. It implies that a barely perceptible difference between two intensities should equal a constant fraction of the higher one. Fechner's law applies principally to intensities ranging between 10 and 100 milli-foot-lamberts. The factor of contrast has been studied extensively by Roelofs and Bierans De Haan,[7] who found that

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McCarthy (Ludvigh, E., and McCarthy, E. F.: Absorption of Visible Light by the Refractive Media of the Human Eye, ARCH. OPHTH. **20**:37 [July] 1938), apparent photopic brightnesses of equal energy sources correspond only to 56.9 per cent of the brightness of the energy directly incident on the retina. In scotopic vision the visibility curve is shifted almost 50 millimicrons in the direction of the short wave end of the spectrum, and the absorption by the ocular media has a more profound effect on the apparent brightness at low intensities than at high. The apparent scotopic brightness of a given energy source has been calculated to be 49.8 per cent of the brightness it would have if the energy were directly incident on the retina.

Allowance should also be made for the absorption of radiant energy by the water vapor of the earth's atmosphere. For average relative transmission during various kinds of weather see F. E. Fowle: Smithsonian Physical Tables, Washington, D. C., The Smithsonian Institute, 1934.

3. Otuka, J.: Difference Between the Visual Acuity in Daylight and in the Dark, Acta Soc. ophth. jap. **44**: 2065, 1940.

4. Hecht, S.: Seeing in a Blackout, Harper's Magazine, July 1942, p. 158.

5. The brightness of the zenith sky on a clear moonless night has been found to be approximately 0.00015 foot lambert.

6. Cobb, P. W., and Moss, F. K.: The Four Variables of the Visual Threshold, J. Frankl. Inst. **205**: 831, 1928.

7. Cited by Troland.[8]

visual acuity varies with the square root of the contrast. Pretori and Sachs,[7] reporting on quantitative measurements of contrasts, stated that contrast increases with the duration of the stimulus.

In light adaptation, the duration of the primary image on the retina varies from 0.05 to 0.2 second. With dark adaptation, the sensitivity of the retina to light is increased, and the duration of the sensation is lengthened. In general the duration of the sensation varies inversely with the brightness of the stimulating light.

As the illumination is diminished, colors manifest a change in their characteristics. Red and orange hues become darker; blue and green hues become brighter. The shift in the sensitivity of the eye toward shorter wavelengths of radiant energy at low brightness levels is called Purkinje's phenomenon. This effect is obviously even more pronounced with colored lights such as red and blue. In black-out lighting, blue as a color is undesirable because it appears brighter than other colors and also because it can be seen by peripheral vision over a greater extent of the visual field than a white light of the same intensity. Red lights are superior to blue because the photochromatic interval, below the threshold of color over a small range of intensities, makes it possible to sense red light as red and not as colorless, which is the way other colored lights appear. For red light, the rods and cones possess nearly the same intensity thresholds. A dimly lit red area can be detected by an observer only when his line of sight passes within a degree or two of it.

OCULAR FACTORS

From the standpoint of the eye, the oculomotor coordination, the errors of refraction, the size of the pupil, the condition of the crystalline lens and the state of the retina and optic nerve are the principal factors affecting visibility.

Previous light adaptation of the retina is still another factor which modifies the performance of the ocular functions when night falls. To achieve critical seeing at night, higher intensities of illumination are required after previous exposure to glare and strong sunlight than after exposure to fog and mist.

The oculomotor functions involved in both day and night vision include fixation, accommodation, convergence and the pupillary reactions.

At the absolute visual threshold, fixation is very difficult and accommodation breaks down completely. Troland[8] stated that for fixation 7.3 by 10^{-10} foot candles and for accommodation 0.0017 foot candle is the minimal intensity of light required.

The convergence reaction is maintained well beyond the brightness range of accommodation provided the eyes are not used solely for scotopic vision over long periods. A decrease in the amplitude of the convergence reserve of 1 to 3 D. has been reported by Luckiesh and Moss[9] in subjects who performed strenuous visual tasks at reduced intensities of illumination.

The pupillary light reflex serves as a distinct aid to seeing in scotopic vision. Engelking designated the threshold for pupillary contraction at 0.003 foot candle. The size of the pupil is of considerable importance in all measurements involving visual acuity. Reeves stated that a logarithmic relation exists between intensity of illumination and the pupillary area. As the pupil increases in size, more light is available at the retina, and the definition of the image is decreased.

8. Troland, L. T.: An Analysis of the Literature Concerning the Dependency of the Visual Functions upon Illumination Intensity, Tr. Illum. Engin. Soc. **26**:107, 1931.

9. Luckiesh, M., and Moss, F. K.: The Science of Seeing, New York, D. Van Nostrand Company, Inc., 1937, p. 277.

Errors of refraction, especially corneal astigmatism, interfere with visibility at low intensities of illumination. Chromatic and spherical aberrations act in a similar manner. This interference decreases in photopic vision.

Opacities of the crystalline lens raise the dark adaptation threshold by diffusion and absorption of incident light rays.

Organic diseases of the posterior segment account for deficient night vision in a large number of persons. Such diseases may be congenital or acquired and can usually be detected on ophthalmologic examination. They comprise retinal detachment, retinal arteriosclerosis, retinitis punctata albescens, glaucoma, choroiditis, retinitis pigmentosa and a host of other conditions.

In the absence of visible pathologic changes within the fundus, night blindness may be due to a disturbance in the metabolism of vitamin A. This type of night blindness is presumed to be due to an insufficient supply or an impaired absorption of vitamin A or to defective conversion of carotene-like substances into this vitamin. Yudkin and his collaborators [10] in experiments on rats showed that the retina is richly supplied with vitamin A. Wald [11] demonstrated that vitamin A enters into the constitution of visual purple. The visual purple constantly undergoes a cycle of breakdown when light falls on the retina and of resynthesis in the dark. In the absence of a fresh supply of vitamin A, the resynthesis is retarded, and the visual threshold of the eye is raised. It has been shown by Hecht [12] that both the cone and the rod threshold are raised by deprivation of vitamin A. Rod vision, however, is affected more than cone vision.

The minimum daily requirements of vitamin A have been set differently by different observers. Jeghers [13] suggested that 4,000 international units represents the daily minimum requirement for a healthy adult. Isaacs, Jung and Ivy [14] calculated that the vitamin A intake of 143 healthy medical students ranged from 1,650 to 9,725 international units per day. Booher and Callison [15] found that between 47 and 57 international units of vitamin A per kilogram of body weight was necessary for the maintenance of normal dark adaptation in normal adults.

In the presence of clinical manifestations of vitamin A deprivation in a group of 20 patients who had no other ocular abnormalities, Feldman [16] administered 20,000 international units of vitamin A daily. Within six weeks all but 2 of his patients showed normal dark adaptation. Flynn [17] prescribed 30,000 international units of vitamin A daily to 32 aviators who showed deficiency in dark adaptation but otherwise were in good physical condition. Twenty-two of the group responded within fourteen days. Yudkin fed 100,000 international units of vitamin A daily for ten days to 24 subjects with night blindness and obtained improvement in all except 3. Getz and his associates recommended doses up to 200,000 international units daily until maximum return of function was obtained. Isaacs and his associates administered doses as high as 300,000 international units of

10. Yudkin, A. M.; Kriss, M., and Smith, A. H.: Vitamin A Potency of Retinal Tissue, Am. J. Physiol. **97:** 611, 1931.

11. Wald, G.: Carotenoids of the Visual Cycle, J. Gen. Physiol. **19:**351, 1935.

12. Hecht, S.: Rods, Cones and the Chemical Basis of Vision, Physiol. Rev. **17:** 239, 1937.

13. Jeghers, H.: The Degree and Prevalence of Vitamin A Deficiency in Adults, J. A. M. A. **109:** 756 (Sept. 4) 1937.

14. Isaacs, B. L.; Jung, F. T., and Ivy, A. C.: Vitamin A Deficiency and Dark Adaptation, J. A. M. A. **111:** 777 (Aug. *27*) 1938.

15. Booher, L. E., and Callison, E. C.: The Minimum Vitamin A Requirement of Normal Adults: II. The Utilization of Carotene as Affected by Certain Dietary Factors and Variations in Light Exposure, J. Nutrition **18:** 459 (Nov. 10) 1939.

16. Feldman, J. B.: Dark Adaptation, Night Blindness and Glaucoma, Arch. Ophth. **22:** 595 (Oct.) 1939.

17. Flynn, V. P.: Clinical Test for Dark Adaptation, J. Aviation Med. **13:** 216, 1942.

vitamin A daily to 3 experimental subjects over a period of four months without any apparent constitutional after-effects.

Individual variations in the ability to absorb, store and utilize vitamin A or its precursor, carotene, may account for the differences which exist between night-blind and night-seeing persons after deprivation of vitamin A. Kimble and Gordon [18] stated that riboflavin and ascorbic acid play a part in the synthesis of visual purple from vitamin A. They found that the daily administration of 200,000 units of vitamin A over a period of two months failed to bring about any improvement in some persons with low vitamin A levels. When the dose of vitamin A was supplemented with 1 mg. of pure riboflavin they obtained an almost immediate rise in the levels of vitamin A in the blood and the patients were subjectively improved. Von Euler and Adler [19] suggested that riboflavin has a special function during twilight, changing short waves into light of a frequency of waves for which the human eye has maximum sensitivity. Pock-Steen [20] reported a syndrome of reduced visual acuity occurring at twilight and under conditions of inadequate artificial illumination. His patients did not respond to vitamin A therapy but improved on the administration of riboflavin. In persons in whom riboflavin failed to produce this result Stewart [21] obtained satisfactory improvement on the addition of ascorbic acid to the vitamin A therapy.

SYSTEMIC FACTORS

The eye is influenced in all of its functions by the physical status of the body as a whole.

Wolfflin [22] suggested that persons with marked pigmentation of the fundus possess better dark adaptation than those with little pigmentation. Matthey [23] disputed this assertion, as she found no difference between the dark adaptation curves of persons with lightly and those with heavily pigmented eyes.

Sex has no effect on dark adaptation.

Advanced age retards the conscious perception of light at low intensities partly because of failing accommodation, miotic pupils and yellowing of the ocular media, and partly because of diminished circulatory efficiency. Ferree, Rand and Lewis [24] studied the influence of age on light requirements. They found that with advancing years higher intensities of illumination had to be provided for the efficient performance of a given task by the same person. Matthey found that lowered dark adaptation of elderly subjects improved with artificially induced mydriasis.

A good deal of night blindness is hereditary. The pedigree published by Cunier Nettleship (after Franceschetti [25]), which includes ten generations, is well

18. Kimble, M. S., and Gordon, E. S.: The Importance of Riboflavin and Ascorbic Acid in the Utilization of Vitamin A, J. Biol. Chem. **128**:111, 1939.

19. von Euler, H., and Adler, E.: Ueber Flavin und einen Blaufluorescierenden Stoff in der Netzhaut der Fischaugen, Ztschr. f. physiol. Chem. **228**: 1, 1934.

20. Pock-Steen, P. H.: Eye Symptoms in Patients with Leiodystomia and Sprue; Aknephascopia, Geneesk. tijdschr. v. Nederl.-Indië **78**: 1986 (Aug. 8) 1939.

21. Stewart, C. P.: Nutritional Factors in Dark Adaptation, Edinburgh M. J. **48**: 217, 1941.

22. Wolfflin, E.: Einfluss des Lebensalters auf den Lichtsinne by dunkeladaptiertem Auge, Arch. f. Ophth. **61**: 524, 1905.

23. Matthey, G.: Eine "Standardkurve" der Dunkeladaptation für klinische Untersuchungen, Arch. f. Ophth. **129**:275, 1932.

24. Ferree, C. E.; Rand, G., and Lewis, E. F.: Age as an Important Factor in the Amount of Light Needed by the Eye, Arch. Ophth. **13**: 212 (Feb.) 1935.

25. Nettleship, C., after Franceschetti, A.: Hereditary Eye Diseases, in Schieck, F., and Brückner, A.: Kurzes Handbuch der Ophthalmologie, Berlin, Julius Springer, 1930, vol. 1.

known. Numerous similar cases are on record in the literature. Riddell [26] recently reported on a family whose members exhibited hereditary stationary sex-linked night blindness.

Fatigue, digestive disturbances, minor infections, tuberculosis and peptic ulcers are associated with various degrees of night blindness. Ezickson and Feldman [27] reported controlled studies of the dark adaptation curves of a group of 25 patients with urinary calculi. They obtained pathologic curves for all but 1. Their patients failed to respond to intensive vitamin A therapy. The authors stated the belief that the pathologic dark adaptation of these subjects was due to lack of assimilation of the vitamin. Haig, Hecht and Patek [28] reported more extensive changes in rod function than in cone function in the dark adaptation of patients with cirrhosis of the liver. This observation is borne out by findings of Wolff [29] and Moore,[30] who reported that the liver is the main reservoir of vitamin A in the body as well as the site of conversion of carotene into vitamin A. Edmund and Clemmesen,[31] using specially constructed test charts, found that pregnant women exhibited reduced "powers of distinction" for the fainter letters. They reported a definite improvement after intramuscular injections of vitamin A.

McFarland [32] noted a decrease in light sensitivity in anoxemia and hypoglycemia which resulted in a depression of both the rod and the cone portion of the curve. He ascribed this change to slowing of the oxidative processes on the nerve tissue rather than to photochemical changes within the retina. Colson [33] found no appreciable effect on the slope of the recovery curve for dark adaptation after ingestion of alcohol. He postulated, however, that alcohol lowers the speed of dark adaptation either by hastening the disintegration of the visual purple or by retarding its formation. Yudkin [34] reported a transient improvement in dark adaptation in patients who were given alcohol and amphetamine (benzedrine) sulfate. He stated that the degree of temporary improvement so produced may even exceed the maximum gain obtained from large doses of vitamin A. McFarland [35] attributed the action of alcohol on the organism to diminished utilization of oxygen in the tissues and called attention to the similarity which exists between anoxemia and alcoholic intoxication.

Endemic outbreaks of night blindness were reported from Denmark during World War I. Similar occurrences have often been encountered in Russia as a result of fasting during Lent.

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26. Riddell, W. J. B.: A Pedigree of Hereditary Stationary Sex-Linked Night Blindness, Ann. Eugenics **10**: 326, 1940.

27. Ezickson, W. J., and Feldman, J. B.: Signs of Vitamin A Deficiency in the Eye Correlated with Urinary Lithiasis: Report of Clinical Studies and Investigation on Twenty-Five Patients, J. A. M. A. **109**: 1706 (Nov. 20) 1937.

28. Haig, C.; Hecht, S., and Patek, A. J.: Vitamin A and Rod and Cone Adaptation in Cirrhosis of the Liver, Science **87**: 534, 1938.

29. Wolff, L. K.: On the Quantity of Vitamin A Present in the Human Liver, Lancet **2**: 617, 1932.

30. Moore, T.: Vitamin A Reserves of the Human Liver in Health and Disease, Lancet **2**: 669, 1932.

31. Edmund, C., and Clemmesen, S.: On Parenteral A Vitamin Treatment of Dysaptatio (Nyctalo-Hemeralopia) in Some Pregnant Women, Acta med. Scandinav. **89**:69, 1936.

32. McFarland, R. A., and Forges, W. H.: The Effect of Variations in the Concentration of Oxygen and of Glucose on Dark Adaptation, J. Gen. Physiol. **24**: 69, 1940.

33. Colson, Z. W.: The Effect of Alcohol on Vision, J. A. M. A. **115**: 1525 (Nov. 2) 1940.

34. Yudkin, S.: Vitamin A and the Dark Adaptation: Effect of Alcohol, Benzedrine, and Vitamin C, Lancet **2**: 787, 1941.

35. McFarland, R. A.: Fatigue in Aircraft Pilots, New England J. Med. **225**: 845, 1941.

A seasonal fluctuation of the dark adaptation curve was reported by Pett,[36] in Canada, who found that approximately half of his 500 subjects showed an impairment of dark adaptation in January as compared with October.

A day to day variation in the rod threshold of 0.2 log unit and in the cone threshold of 0.3 log unit, presumably due to variations in the blood sugar content, was reported by Yudkin.

PSYCHOLOGIC FACTORS

In addition to physiologic factors, there are psychologic reactions directly attributable to the surroundings which figure in the performance of visual tasks at inadequate levels of illumination. Attitude, enthusiasm and alertness are but a few of the variables which influence the ability to see at night.

Wittkower and Rodger [37] examined 42 soldiers who complained of night blindness. Only 1 exhibted demonstrable ocular disease and a pathologic dark adaptation curve. On psychologic examination, more than half of the group showed chronic anxiety states. The authors concluded that in most cases of night blindness in England the condition is probably on a psychologic basis.

From a neurologic standpoint Bruckner [38] asserted that only dark-adapted eyes are capable of summation of impressions of the two eyes and that this faculty is absent in light-adapted eyes even when stronger stimuli are used. He placed the summation of the stimuli, as the correlative of the psychic sensations, in the corpus geniculatum laterale, in the visual cortex of the posterior lobe or even higher. He called attention to the possibility of a reciprocal relationship between the brain and the retina and suggested that the important part played by the phenomenon of contrast in night vision may be explained by this relationship.

DELETERIOUS EFFECTS

In certain persons prolonged and at times temporary visual effort in the dark will precipitate eyestrain and functional inefficiency, will predispose to accidents and may even result in organic damage. Eyes which have to work under inadequate and unsteady illumination for any length of time soon become fatigued.

Meyer [39] stated that poor vision, whether due to insufficient light or to uncorrected ocular defects, is one of the principal factors responsible for ocular as well as for bodily fatigue.

Jeghers called attention to the high incidence of automobile accidents, and the medicolegal implications arising therefrom, among drivers with impaired night vision.

I have witnessed scores of minor and major accidents in the homes of a community where rigid regulations for total black-out have been continuously enforced for almost one year.

Tinker [40] showed that visual fatigue becomes manifest when less than 3 foot candles of well diffused light are available for reading.

Berens [41] said: "Unsteady variable and flickering illumination, forcing the eyes to readjust themselves constantly under the varying conditions of seeing,

36. Pett, L. B.: Vitamin A Deficiency: Its Prevalence and Importance as Shown by a New Test, J. Lab. & Clin. Med. **25**: 149 (Nov.) 1939.

37. Wittkower, E., and Rodger, T. F.: "Night Blindness," Psychophysiological Study, Brit. M. J. **2**: 571, 1941.

38. Bruckner, A.: Physiologic and Clinical Ophthalmologic Problems in Relation to Individual Variability, Arch. Ophth. **20**:726 (Nov.) 1938.

39. Meyer, L. L.: Eyesight in Industry, Arch. Ophth. **27**: 275 (Feb.) 1942.

40. Tinker, N. A.: Illumination Standards for Effective and Comfortable Vision, J. Consult. Psychol. **3**: 11, 1939.

41. Berens, C.: Eyes in Industry, Hygeia **16**: 125 (Feb.) 1938.

may also cause eye fatigue. Shadows caused by clouds and smoke may cause annoying variations in light. Flickering which results from a varying current is extremely tiring."

Bockoven and Wilcox [42] stated that retinal fatigue occurs first when the subject is viewing red objects; then, in order come yellow, blue, white and green.

The rate of blinking has been adopted by numerous investigators as a fairly reliable index for recording visual and, indirectly, bodily fatigue. Luckiesh and Moss obtained a definite rise in the blink rate in subjects who were required to perform increasingly arduous tasks at decreasing intensities of illumination.

Luckiesh and Moss also reported a slowing of the pulse rate and an increase in the neuromuscular tension of the body in persons who read with 1 foot candle, as compared with 100 foot candles, of illumination.

Coiger,[43] reporting on 400 cases of miner's nystagmus, expressed the belief that the oscillations were due to prolonged work at low (scotopic) levels of illumination. He found that the oscillations were accompanied by complaints of headaches and dizziness and were in most instances complicated by psychic disturbances.

Tansley [44] postulated that in certain cases of night blindness resulting from vitamin A deficiency irreversible degenerative changes may be produced in the rods. If this supposition is true, it may explain the slowness or absence of response in some persons to large doses of carotene or vitamin A.

According to Tijssen,[45] chronic severe deprivation of vitamin A is the third most frequent cause of blindness in the Netherland Indies. This syndrome begins with night blindness and xerosis and progresses to xerophthalmia, keratomalacia and ultimate loss of sight.

METHOD OF EXAMINATION

Ophthalmologic examinations performed under photopic brightnesses measure principally the functions of the retinal cone cells; to evaluate rod function, the tests must be performed with the eyes in the dark-adapted state.

Most of the better known instruments used for testing night vision measure the minimum brightness required to render a given surface visible and the speed or range of adaptation from light to darkness. From a practical standpoint, however, the ability to discriminate detail and the ability to recognize lights of faint brightnesses throughout the entire retina are of greater importance than the amount, range and speed of dark adaptation.

A few of the instruments and charts described in the literature for investigating ocular functions at scotopic brightnesses include those devised by the following authors [46]:

Bjerrum [47] was among the first to construct a special Snellen chart with reduced contrast between the type and the background.

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42. Bockoven, S., and Wilcox, B.: Significance of Retinal Fatigue in the Study of General and Nervous Disease, Arch. Ophth. **17**: 1024 (June) 1937.

43. Coiger, H.: Miners' Nystagmus, M. Press **206**: 152, 1941.

44. Tansley, K.: The Effect of Vitamin A Deficiency on Development of Retina and on First Appearance of Visual Purple, Biochem. J. **30**: 839, 1936.

45. Tijssen, J.: Value of Medicinal Therapy of Ocular Avitaminoses (Xerophthalmia and Keratomalacia) in Netherland Indies, Geneesk. gids **18**: 936, 1940.

46. The test chart accepted in accordance with the specifications of the Advisory Committee of Ophthalmologists of the Eye Health Committee of the American Student Health Association acting in cooperation with the National Society for the Prevention of Blindness requires a uniform brightness of 10 foot lamberts.

47. Bjerrum, J.: Untersuchungen über den Lichtsinn und den Raumsinn bei verschiedenen Augenkrankheiten, Arch. f. Ophth. **30**: 201, 1884.

Edmund and Moller designed a chart composed of a series of letters ranging from black to light gray on a white background. They evaluated their subject's ability to recognize the faintest letters and expressed their findings by the term "power of distinction." They found that the power of distinction of a given subject varied directly with the intensity of illumination of the test chart.

Jeans, Blanchard and Zentmire [48] described an instrument known as the biophotometer. With it they measured the light threshold and the rate and degree of dark adaptation. Their instrument was criticized by Isaacs, Jung and Ivy [49] and by Palmer and Blumberg.[50] These investigators, in separate studies, pointed out that in their hands the biophotometer gave inconsistent and uncertain results on successive readings.

An instrument originated by Ferree and Rand [51] makes it possible, according to the authors, to determine the acuity, rate and amount of dark adaptation as measured by changes in the amount of light required for discrimination of a test object. With the Ferree-Rand instrument, determinations may be made at reproducible intensities of illumination from very low to the brightness equivalent of 100 foot candles on an ordinary chart. The intensity of light delivered may be read directly or readily derived from the scale of the instrument.

More recently Hecht and Schlaer [52] constructed an adaptometer for the measurement of dark adaptation. This instrument has gained wide acceptance and in my opinion is the best available adaptometer at the present time.

Flynn employed a simple instrument which measures the ability of the retina to regenerate visual purple after it has been exposed to a bright light. The instrument consists of two bulbs of 5,400 millilamberts each placed 3 feet (91 cm.) from the observer's eyes. The subject is asked to look at the bright light for three minutes. The light is then turned off, and he is directed to look at a test light possessing a brightness of 0.004 millilamberts placed 18 inches (46 cm.) from his eyes. In testing a series of 500 pilots between 18 and 50 years of age, Flynn found that an average of sixty seconds elapsed after the bright light was turned off and the test light recognized.

Luckiesh and Moss's [53] low contrast test chart approximates brightnesses that prevail on roads and highways at night. With this chart they were able to measure visual acuity at intensities as low as 0.01 foot lambert.

Harman [54] introduced a simple inexpensive means of testing light sensitivity at low brightnesses. The light in his instrument emanates from a standard candle burning 120 grains (8 Gm.). It is mounted inside a black box. This furnishes a standard beam of light which illuminates a test card placed at 5 meters. The test card consists of a board 1 foot (30 cm.) square covered with black velvet. The test objects are white disks ½ inch (1.3 cm.) in diameter arranged ⅛ inch

48. Jeans, P. C.; Blanchard, E., and Zentmire, A.: Dark Adaptation and Vitamin A, J. A. M. A. **108**: 451 (Feb. 6) 1937.

49. Isaacs, B. L.; Jung, F. T., and Ivy, A. C.: Clinical Studies of Vitamin A Deficiency: Biophotometer and Adaptometer (Hecht) Studies on Normal Adults and on Persons in Whom an Attempt Was Made to Produce Vitamin A Deficiency, Arch. Ophth. **24**:698 (Oct.) 1940.

50. Palmer, C. E., and Blumberg, H.: The Use of a Dark Adaptation Technic (Biophotometer) in the Measurement of Vitamin A Deficiency in Children, Pub. Health Rep. **52**: 1403 (Oct.) 1937.

51. Ferree, C. E., and Rand, G.: Visual Acuity at Low Illuminations: Apparatus and Results, Tr. Am. Ophth. Soc. **17**:370, 1919.

52. Hecht, S., and Schlaer, S.: An Adaptometer for Measuring Human Dark Adaptation, J. Optic. Soc. America **28**: 269, 1938.

53. Luckiesh, M., and Moss, F. K.: The Ability to See Low Contrasts at Night, J. Aeronaut. Sc. **9**:261, 1942.

54. Harman, N. B.: Testing Night Vision, Brit. M. J. **1**:636, 1941.

(0.3 cm.) apart in groups ranging from four to seven. The room is darkened except for the candle rays. The object is to find the maximum distance at which the patient can count the spots accurately. Harman [55] contended that by altering the size of the disks or varying the intensity of the light his test may be employed for detection of suspected shamming of night blindness. If the disability is genuine, vision should improve when more light or larger disks are used; if the disability is false, vision will diminish when less light and smaller disks are provided.

An ingenious device based on sound physiologic principles for the study of regional appreciation and differences in the light sense has been described by Louise L. Sloan.[56] She takes full cognizance of the central scotoma which prevails under scotopic brightnesses and which precludes accurate central fixation. Her instrument is equipped with a special foveal fixation device mounted on a Ferree-Rand perimeter for making determinations 6 degrees or more from the fovea and with a perifoveal fixation device for measuring the light sense at the fovea. The former consists of a red filter inserted between the light source and the target and a rheostat connected in series with the lamp to regulate the brightness of the target for each patient. The target consists of four spots of radium paint placed so that they fall just at the edges of the blindspot, determined in light adaptation, for a given direction of fixation. The advantages of this test are listed by Sloan as follows:

> (*a*) The thresholds may be determined at intervals from the center to the periphery with the perimeter lamp lighted. . . . (*b*) Similar determinations may be made in the dark, after the eye has reached a more or less steady state of dark adaptation. The difference in thresholds, in logarithmic units . . . gives a measure of the increase in sensitivity with dark adaptation at each of the regions of the retina tested. (*c*) The adaptation curve, showing the rate of increase in sensitivity with dark adaptation, may be determined for any selected region of the retina.

A test which may be used as an auxiliary means of studying night vision and serve as an aid in the detection of malingerers has been suggested by Riddel.[57] It is based on the finding that the last four plates of Schilling's color book are usually incorrectly named by the night-blind person. These four plates are designed for the detection of disturbances of yellow-blue sensitivity. Good daylight illumination is essential during the performance of this test.

DEFINITIONS [58]

A short list of definitions of some commonly employed lighting terms is appended with the hope that the universal adoption of an adequate and rational terminology may promote a better understanding and closer cooperation among investigators entrusted with the manifold problems of night vision facing the civilian and military populations.

Candle.—The unit of light intensity. The unit used in the United States is a specified fraction of the average horizontal candle power of a group of forty-five carbon filament lamps preserved at the National Bureau of Standards when the lamps are operated at specified voltages.

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55. Harman, N. B.: Shamming Night Blindness, Brit. M. J. **2**: 737, 1941.

56. Sloan, L. L.: Instruments and Technics for the Clinical Testing of Light Sense: III. An Apparatus for Studying Regional Differences in Light Sense, Arch. Ophth. **22**: 233 (Aug.) 1939.

57. Riddell, W. J. B.: Two Clinical Tests for Night Blindness, Tr. Ophth. Soc. U. Kingdom **60**: 181, 1940.

58. Roget, S. R.: A Dictionary of Electrical Terms, ed. 3, New York, Pittman Publishing Corporation, 1938. Warren, W. C.: Dictionary of Psychology, Boston, Houghton, Mifflin Company, 1934.

Candle Power.—Light intensity expressed in candles.

Foot Candle.—The unit of illumination when the foot is taken as the unit of length. It is the illumination on a surface 1 square foot (900 sq. cm.) in area over which 1 lumen is uniformly distributed.

Lumen.—The unit of light quantity. A uniform point source of one candle emits 12.56 lumens.

Lambert.—A unit of brightness of an ideal white surface receiving 1 lumen per square centimeter equal to 0.718 candle per square centimeter.

Foot Lambert.—A unit of brightness equal to the average brightness of any surface emitting or reflecting 1 lumen per square foot.

Lux or Meter Candle.—The illumination of a surface receiving 1 lumen per square meter.

Photopter.—The illumination of a surface receiving 0.1 lux.

Photon.—A unit of retinal illumination. It is 1 candle per square meter per square millimeter of pupillary aperture.

Visibility.—The intensity of a stimulus which evokes visual perception and discrimination.

Brightness.—The luminous intensity emitted by a surface in a particular direction per unit area projected in that direction.

SUMMARY AND CONCLUSIONS

The mechanism of night vision has been reviewed. The effects of contrast, brightness, size and time on this function have been estimated. Attention has been called to the roles played by the ocular, physical and psychologic states of the subject in determining his ability to see at night. Harmful consequences arising from disturbances of the scotopic mechanism have been discussed. A few of the more generally accepted methods of examination have been described. The desirability of investigating the ability to discriminate detail and recognize lights throughout the visual field, instead of merely measuring the speed and range of dark adaptation, has been stressed. A list of definitions of lighting terms has been included.

1013 Bishop Street.

Correspondence

EIKONOMETER AND COMPARATOR

To the Editor:—Captain Field's paper "A Comparison of Ocular Imagery," in the June issue (ARCH. OPHTH. **29:** 981, 1943), "consists of a comparison of two instruments," the eikonometer and the comparator. Details of the construction and mode of action of the comparator are not given (patents are pending), so that one must confine one's criticism to the results as published. Fortunately, these are ample to demonstrate that the data obtained by the comparator are of no value.

The "sensitivity" of each instrument is recorded for 25 subjects with 20/20 vision with or without correction. The refractive corrections are not recorded, nor is the heterophoria as measured by an independent test, such as the cover test or rod test. Fifty readings with the comparator and 52 with the eikonometer are recorded.

The sensitivity was of great significance in this as in other experiments. It is what the laboratory workers call the "just noticeable difference," "j. n. d.," and shows the limits of accuracy, the limits of dependability, of a given test. Thus a balance may weigh with an accuracy of ± 1 mg., another may weigh with an accuracy of ± 0.1 mg., and so on; a constant temperature oven is guaranteed to maintain a given temperature ± 0.5 C., or a constant temperature bath may be guaranteed not to vary more than ± 0.005 C. With the eikonometer, in only 3 observations was the range more than ± 1 per cent; in 10 it was ± 0.25 per cent, which is excellent. In 49 of 52 observations, the range was equal in the two directions, + and —. Normally of course it should be equal. If it is not or if the amount is over 1 per cent, further investigation is called for.

I wish to point out certain astonishing data that are given for the comparator. In every observation but one the range was more than ± 1, and in the other observation on the same eye the range was + 2.9 to — 11 per cent. I did not take the trouble to average the values, but the range in 9 observations was 10 per cent or over and in 1, case 20, over 20 per cent!

In only 1 observation on the comparator were the plus and minus deviations equal; viz., case 10 (+ 6.1 and — 6.1). In most of the cases the plus shift was entirely different from the minus shift, for example: + 2.9, — 11.1; + 1.2, — 8.2; + 3.1, — 13.; + 1.8, — 13.7, or + 0.7, — 16.3. Perhaps the significance would be more apparent if the same plan was applied to measuring refraction. Suppose an instrument were seriously offered which gave such results as the following: The refraction is determined to be + 2.70 D. ± 6.1 D. That is, the refraction is + 2.7 D., but if the lens is made stronger and stronger the change is not detected on this instrument until + 8.8 D. is reached, and if the lens is made weaker and weaker the change is not noticed until the lens is reduced to — 3.4 D. Consider the absurdity of proposing to measure aniseikonia with an instrument whose margin of error is several times as large as the quantity to be measured, often five times even ten times as large, and in which the chosen reading is practically never in the middle of the range, i. e., the plus deviation is never equal to the minus!

The kindest criticism is to say that the author has no adequate conception of what he is trying to measure and no experience in laboratory measurements, and there is other evidence in the paper to support that view.

Thus, the two targets are respectively 4 degrees in the eikonometer and 39 minutes in the comparator. At 457 cm., the distance used, this means the size of the eikonometer target was (tan 4 degrees at 457 cm.) 31.89 cm. and the size of the comparator target was (tan 39 minutes at 457 cm.) 5.18 cm. One per

cent of the eikonometer target was 3.19 mm., about ⅛ inch; 1 per cent of the comparator target was 0.5 mm., about 1/50 inch. Thus, to recognize a 1 per cent difference between the two targets as seen one with the right eye and the other with the left means to detect with the eikonometer ⅛ inch at 15 feet (457 cm.) or to detect with the comparator 1/50 inch at 15 feet (457 cm.). The 15/15 Snellen letter is about ¼ inch (0.64 cm.) over all. The comparator calls for detection of 1/50 inch at 15 feet. No wonder the subject is uncertain whether the difference in size is 1/50 inch or ten times as much, ⅕ inch (0.5 cm.).

It is hard to believe that any one could seriously advocate such a device.

As a means of measuring heterophoria the comparator as recorded is very misleading. Of 25 subjects 18 showed right hyperphoria, and that of 13 was over 0.5 prism diopter. Exophoria was usually less than that shown by the eikonometer, especially if amounts less than 0.5 prism diopter were neglected. Esophoria was always larger than that shown by the eikonometer.

Thus internal evidence shows the comparator to be very misleading in measuring heterophorias, recording far too many right hyperphorias (as the author himself points out). Also, there is a tendency to convergence when the subject looks into the machine, as all esophorias were too large and most exophorias too small.

Finally, the author speaks of the eikonometer target as falling "within the macular area of fixation," thus revealing his ignorance of the fact that the central device of the eikonometer target is designed to fall on the periphery of the retina and only the small dashes to fall on the fovea, the validity of this arrangement being dependent on the dominance of peripheral fusion (Burian, H. N.: Fusional Movements in Permanent Strabismus, ARCH. OPHTH. **26:** 626 [Oct.] 1941; Lancaster, W.: A Reply to Criticisms of Aniseikonia, *Tr. Am. Ophth. Soc.* **40:** 82, 1942).

The author seems not to know that heterophoria is universal and that aniseikonia is also universal. It is only a question of how small amounts one wishes to take account of. With the cover test, of course, small heterophorias are not detectable, but there are various ways, not used clinically, of showing small deviations. Ametropia also is universal; emmetropia exists only if one neglects small departures from the ideal, imaginary condition of emmetropia.

Thus the question in aniseikonia is the same as in heterophoria and refraction, not, Does it exist? but, Is it present in sufficient amount to call for correction? and Shall ophthalmologists continue to correct defects in the order heretofore followed, viz. first refraction, second heterophoria and third aniseikonia, without neglecting other methods of treatment?

The author finds that there is a close relationship between heterophorias and aniseikonia and says that the comparator offers a possibility of segregating these two elements. How can this be possible when the instrument is incapable of measuring either aniseikonia or heterophoria? I wish the author would study the paper in the *Transactions of the American Ophthalmological Society* previously cited.

WALTER B. LANCASTER, M.D., Boston.

520 Commonwealth Avenue.

News and Notes

EDITED BY DR. W. L. BENEDICT

GENERAL NEWS

Research Chair at Royal Eye Hospital.—The Royal College of Surgeons has founded a research chair in ophthalmology tenable at the Royal Eye Hospital, Southwark (in London). It is the first chair of the kind in this country, and the hospital has undertaken to raise $200,000 for its permanent endowment. The holder of the chair will devote the whole of his time to clinical research at the hospital and to laboratory work at the Royal College of Surgeons.

Course in Gonioscopy.—The Eye and Ear Research Fund, Inc., announces a two day course in practical gonioscopy to be given at the Illinois Eye and Ear Infirmary after the meeting of the American Academy of Ophthalmology and Otolaryngology. The course will begin October 14 at 9 a. m. and will end October 15 at 5 p. m. Applications and requests for particulars should be addressed to the dean of instruction, 904 West Adams Street, Chicago.

Discontinuance of Graduate Course.—The Department of Ophthalmology of New York University College of Medicine announces that because of the educational program associated with the war effort the nine month graduate course in ophthalmology will be discontinued for the duration of the war.

UNIVERSITY NEWS

University of Nebraska.—The following appointments have been made at the University of Nebraska College of Medicine: Dr. J. Hewitt Judd, professor of ophthalmology and chairman of the department of ophthalmology; Dr. Harold Gifford, associate professor, and Dr. W. Howard Morrison, assistant professor.

SOCIETY NEWS

Pacific Coast Oto-Ophthalmological Society.—The thirtieth annual meeting was held at Portland, Ore., May 11 to 13, 1942, under the presidency of Dr. R. A. Fenton. The principal address of the ophthalmologic section was on "Virus Diseases of the Eye," by Dr. Phillips Thygeson. The following additional papers were presented: "The Sulfonamide Compounds in the Treatment of Ocular Infections: A Review," Dr. Phillips Thygeson; "A Review of Diagnosis and Treatment of 500 Orthoptic Cases," Dr. Bernard G. Barkwill; "The Perimetric Diagnosis of Intracranial Tumors," Dr. John Raaf; "A New Impression Tonometer," Dr. David G. Harrington; "Safety in Cataract Extraction," Dr. Lawrence G. Dunlap; "A Combined Ptosis Operation," Dr. Orwyn H. Ellis, and "Aniseikonia: A Review of 200 Consecutive Cases Examined on the Eikonometer," Dr. Avery M. Hicks.

The following officers were elected for the ensuing year: president, Dr. Donald H. O'Rourke, Denver, and secretary-treasurer, Dr. C. Allen Dickey, San Francisco. The next meeting will be held in the Yosemite National Park, California, in 1943.

Abstracts from Current Literature

EDITED BY DR. WILLIAM ZENTMAYER

Conjunctiva

REGARDING THE EARLY DETECTION OF AVITAMINOSIS A BY GROSS OR BIOMICROSCOPIC EXAMINATION OF THE CONJUNCTIVA. M. L. BERLINER, Am. J. Ophth. **25:** 302 (March) 1942.

Berliner concludes: "I do not consider (1) that the observations made by Kruse on the conjunctiva represent prexerotic states or states possibly indicating an avitaminosis A, but that they represent common presenile and senile alterations; (2) that the 'spots,' or pingueculae, are subepithelial infiltrations, the epithelium over them being unaffected, a condition different from xerosis in which the changes are in the epithelium, and that such spots are not associated with low states of vitamin A, as proved by blood tests; (3) that until such time when more accurate methods of colloidimetry and micrometry are employed and standards created, no accurate deductions can be made concerning the myriad variations in thickness and relucency of the normal conjunctiva; (4) and finally that it is not even certain that all cases of prexerosis, xerosis, and Bitot's spots—that is, those not preceded by preëxisting conjunctival disease, such as, for example, trachoma or pemphigus —are due to vitamin-A deficiency."

W. S. REESE.

Congenital Anomalies

DEFICIENCY OF THE MALAR BONES WITH DEFECT OF THE LOWER LIDS. I. MANN and T. P. KILNER, Brit. J. Ophth. **27:** 13 (Jan.) 1943.

Mann's patient was a boy aged 11 years. The upper lids were normal but drooped downward at the outer ends owing to the defect of the lower lids; a false appearance of squint was given in some positions, since the eyes were not in the centers of the palpebral apertures. There were no ocular defects. The outer 2 or 3 mm. and the outer canthus were normal, but the rest of the lid was thin and atrophic looking and showed no marginal differentiation, the lashes, meibomian glands and intermarginal strip being absent. The lower bony margin of the orbit was defective and the cheek depressed. The fibers of the orbicularis muscle were absent at the inner canthus and along the lower lid. A small bony boss could be felt under the skin at the anterior end of the zygoma.

The external ears were well formed, but the boy was deaf probably owing to malformation of the middle and possibly of the inner ear. The upper jaw was narrow, and there were abnormalities in the spacing of the teeth. Roentgenograms showed defective development of all the facial bones. In particular, the malar bones were small and malformed. (Details of the roentgenograms are given.)

Embryologically the case is described as one of retardation of differentiation of maxillary mesoderm at and after the 50 mm. stage and considered as offering further evidence for the supply of the outer 2 or 3 mm. of the lower lid by the first division of the fifth cranial nerve.

Kilner's patient when first seen was 14. There was no family history of congenital bony defects. The child had been three weeks premature. The mother gave a history of having been frightened by a dog when three months pregnant. Beside the ocular defects, there was a cleft soft palate, crumpling of both ears forward and poor development of the pinna. The external auditory canal was absent on each side. The eyes sloped downward at the outer ends. There was a peculiar angulation of the lower eyelids, with small bushy collections of eyelashes

at the junction of the outer and middle thirds of the lids. There were deep depressions in the infraorbital regions.

A triangular skin flap was transposed from the upper to the lower eyelid across the outer canthus with the object of raising the outer angle of the palpebral fissure, giving some support to the lower eyelid and providing better protection for the eye.

The article is illustrated.

W. ZENTMAYER.

Cornea and Sclera

A THIRD ENTITY OF PRIMARY SYMMETRICAL FATTY CORNEAL DYSTROPHY. J. A. CONWAY and A. LOEWENSTEIN, Brit. J. Ophth. **27**: 49 (Feb.) 1943.

The patient, an unmarried woman aged 35, for twenty years had "kidney trouble" and enlargement of the thyroid. Both eyes were slightly exophthalmic. There were four pingueculas of considerable size and sulfur-like color. In the conjunctiva the red blood corpuscles disappeared in some apparently empty vessels. There was a broad lipoid arch 1 to 1.3 mm. in width not reaching to the limbus, with a hazy area between the arch and the sclera. The peripheral margin of the arc was irregular, reminding one of the ice lumps of cinguliform dystrophy. The authors believe this to be an undescribed entity and place it among the "feeding" fatty dystrophies as a corneal oversupply of fat from the blood stream. They assume that it is the long-lasting lipemia which allows the fatty infiltration. There is a second supposition possible—a lowered corneal metabolism, a deficiency in oxidizing power arising from an altered endocrine balance. The whole cornea was equally infiltrated by small grayish white dots. They extended from a subepithelial level throughout the whole thickness of the corneal lamellas. They covered the whole extent of the cornea. There were no other abnormalities of the cornea. Gunn's dots were present in the retina. The corrected visual acuity was 6/5. The blood urea was high, the cholesterol slightly increased, the albumin low and the globulin high. The albumin-globulin ratio was low.

The article is illustrated.

W. ZENTMAYER.

NOTES ON FORMS OF KERATITIS PRESUMABLY DUE TO THE VIRUS OF HERPES SIMPLEX. J. B. HAMILTON, Brit. J. Ophth. **27**: 80 (Feb.) 1943.

Sixty-three per cent of the keratitis in Australians in the Middle East is due to the virus of herpes simplex; in the majority of cases it is due to a preceding true or artificial pyrexia or to gross change of climate. Repeated painting with 2 per cent silver nitrate is strongly indicated in the treatment of marginal and superficial punctate keratitis; phenolization is still the treatment par excellence for dendritic ulcer. Local application of heat, or thermotherapy of any type, is strongly contraindicated in the treatment of keratitis due to herpes simplex; use of atropine is not necessary except for disciform keratitis.

The article is illustrated.

W. ZENTMAYER.

Experimental Pathology

EXPERIMENTAL PRODUCTION OF PRIMARY OPTIC ATROPHY IN MONKEYS BY ADMINISTRATION OF ORGANIC ARSENICAL COMPOUNDS. B. J. LONGLEY, N. M. CLAUSEN and A. L. TATUM, J. Pharmacol. & Exper. Therap. **76**: 202 (Nov.) 1942.

Longley, Clausen and Tatum tried to determine whether sodium arsanilate and the contributing agents tryparsamide, 3-amino-4-beta-hydroxyethoxyphenylarsonic acid (arsenical no. 190) and acetarsone are capable of producing blindness in monkeys with an intact and normal central nervous system. The eyes of rhesus monkeys resemble the human eye far more closely than those of the rabbit. Such an anatomic relationship might be expected to be paralleled by a similar reactivity.

but experimental work can only suggest what might happen in man, and only careful clinical study will reveal what actually does happen. The administration of sodium arsanilate, tryparsamide, acetarsone, 3-amino-4-beta-hydroxy-ethoxy-phenylarsonic acid (no. 190) and 4-β-(β'-hydroxy)-ethoxyethoxy-phenylarsonic acid (no. 266), the last containing no nitrogen in the molecule, did cause blindness in monkeys. The work provides an experimental basis for detection of the blinding potentialities of arsenical compounds for man. Now prophylactic procedures designed to reduce or eliminate atrophy of the optic nerve as a sequal of chemotherapy of neurosyphilis must be looked for.

J. A. M. A. (W. ZENTMAYER).

General Diseases

OCULAR COMPLICATIONS IN RELAPSING FEVER. J. B. HAMILTON, Brit. J. Ophth. **27:** 68 (Feb.) 1943.

The author reports 9 cases of ocular complications in relapsing fever. In all 4 of the cases in which there was iridocyclitis the fever had been contracted in Tobruk (Libya) or the Western Desert. In only 2 was the spirochete isolated. In the 4 cases in which there was uveitis, there were, respectively, five, three, three and five relapses before the cyclitis appeared. In all the cases the ocular complication was unilateral. No case of optic neuritis was observed; facial paralysis was present in 1 case. Headaches are a worrying complication. Iridocyclitis occurs probably in 20 per cent of cases of relapsing fever.

W. ZENTMAYER.

CIRCUMCORNEAL INJECTION AS SIGN OF RIBOFLAVIN DEFICIENCY IN MAN: ACCOUNT OF THREE CASES OF ARIBOFLAVINOSIS. H. SCARBOROUGH, Brit. M. J. **2:** 601 (Nov. 21) 1942.

Among 204 persons between 12 and 69 years of age seen in the outpatient department from October 1941 to March 1942, when the nutritional deficiency might be expected to be at its peak, Scarborough observed that 70 had circumcorneal injection. This sign occurred with relatively greater frequency among the older patients; 43 of 63 persons older than 50 were affected. The observation of Sydenstricker and his co-workers that circumcorneal injection occurs in ariboflavinosis has been confirmed, but a form of the condition exists even in subjects presenting evidence of frank vitamin deficiency which cannot be attributed to a deficiency of riboflavin because it is not cured by administration of the vitamin. This observation no doubt accounts for the relatively high incidence of circumcorneal injection observed. Although circumcorneal injection may be an early stigma of ariboflavinosis, it cannot be so considered unless it is supported by the presence of cheilosis, glossitis, dermatosis and ocular symptoms or by the results of slit lamp examination of the cornea. Certain subjects manifest a requirement for riboflavin which, for reasons unknown, is unusually large. Clinically, the circumcorneal injection differs in no material way from that described by Sydenstricker as occurring with frank ariboflavinosis.

J. A. M. A. (W. ZENTMAYER).

Glaucoma

RESULTS OF GLAUCOMA SURGERY. S. A. FOX, Am. J. Ophth. **26:** 31 (Jan.) 1943.

Fox gives the following summary and conclusions:

"1. Results are reported in 54 cases of primary glaucoma followed from one-half to six years after operation; over 60 per cent were observed from two to six years. Reduction of tension to normal was obtained in 39 or 72.2 per cent of the cases.

"2. Of 31 cases of chronic congestive glaucoma, normal tension was obtained in 22 (70.9 per cent), vision remained the same in 17 (54.8 per cent), and fields were maintained in 13 (41.9 per cent).

"3. In 12 cases of chronic simple glaucoma normal tension was obtained in 9 (75 per cent), vision remained the same or better in 7 (58.3 per cent), and fields were maintained in 6 (50 per cent).

"4. In 11 cases of acute congestive glaucoma normal tension was obtained in 8 (72.7 per cent).

"5. A review of the published statistics for the past 15 years shows an over-all reported average of 'success' in approximately 75 per cent of cases following glaucoma surgery. This figure is almost identical with the results reported by Wilmer for the previous 15-year period.

"6. The reported over-all average of successful results following the newer and combined operative procedures is 78.2 per cent. This figure is less significant because of fewer cases reported and shorter follow-ups.

"7. During the 15-year period ending in 1927, trephining was the most common operation used in glaucoma surgery, according to the reported statistics. Cyclodialysis and then anterior sclerectomy were next in popularity.

"8. During the following 15 years reports show that trephining still is the most popular choice with the iris-inclusion technique the second most common choice.

"9. On the bases of published figures the iris-inclusion technique has given the best results during the past 30 years.

"10. On the whole, better results appear to have been obtained in the chronic congestive than in the chronic simple glaucomas.

"11. The figures also seem to show that iridectomy is used about as frequently in the chronic as in the acute glaucomas, with poorer results in the former.

"12. Ophthalmology has made poor statistical use of its human operative material. Because of lack of uniformity, published results of glaucoma surgery are of little help in gauging the value of the various procedures and in the solution of the many existing surgical problems in glaucoma.

"13. A program to facilitate the evaluation of published results of glaucoma surgery is suggested.

"14. A simple method for the preoperative clinical classification of chronic glaucoma is suggested."

W. S. REESE.

Hygiene, Sociology, Education and History

CLOVES, OIL OF CLOVE AND EUGENOL: THEIR MEDICODENTAL HISTORY. E. J. MOLNAR, Dent. Items Interest, June, July, August, September and October, 1942.

Molnar gives an interesting account of the use of cloves, oil of clove and eugenol in medicine and dentistry. He states that Honain, author of the first systematic ophthalmologic textbook, endorsed the use of cloves for the treatment of weak eyes. Baithar spoke of cloves as belonging to a special group of drugs used for the eyes. In the writings of von Megenburg is mentioned among the medical uses of cloves that it is "good for the eyes."

Dorstenius in his work on botany mentioned cloves as being of therapeutic value in the treatment of ocular diseases. Molnar states that the first ophthalmologic text in the German language, published at the end of the sixteenth century, contains many references to cloves as a much prescribed medicant for the eyes.

W. ZENTMAYER.

Ocular Muscles

SEX-LINKED HEREDITARY NYSTAGMUS. R. W. WAGGONER and D. A. BOYD, Am. J. Ophth. **25:** 177 (Feb.) 1942.

Waggoner and Boyd report on a family with nystagmus which was transmitted by unaffected females to males. They discuss the modes of inheritance of nystagmus and the possibility of its evidence as a heredofamilial degenerative diathesis.

W. S. REESE.

CONTRACTURE IN OCULAR-MUSCLE PARALYSIS. R. O'CONNOR, Am. J. Ophth. **26:** 69 (Jan.) 1943.

O'Connor advises that in cases of paralysis of an ocular muscle a transplantation operation be done before contracture of the opposing muscle occurs. One should make a test for contracture every week by grasping, with the eye under local anesthesia, the tendon and noting whether resistance is felt when traction is exerted.

W. S. REESE.

VOLUNTARY CONVERGENCE. W. R. MATHEWSON, Brit. J. Ophth. **27:** 34 (Jan.) 1943.

The method employed by Mathewson in exercising convergence consists in (1) placing increasingly strong prisms in the trial frame in series and having the patient look at a light 6 meters away; (2) having the patient alternately approach to within 1 meter of the light and back away to 6 meters, and (3) placing the prisms base out and raising and lowering the frame, instructing the patient to make the two lights into a single image. The last brings about voluntary efforts of convergence. Prisms with bases out are given to be worn at home; thus the exercises are continued at home and the eyes forced to converge.

While claiming nothing novel for these exercises, the author believes that unless the raising and lowering of the prisms is used the cure is not so successful or permanent.

W. ZENTMAYER.

Refraction and Accommodation

A POSSIBLE FALLACY IN THE USE OF THE CROSS-CYLINDER. F. A. WILLIAMSON-NOBLE, Brit. J. Ophth. **27:** 1 (Jan.) 1943.

Williamson-Noble states that if a patient's vision is fogged he tends to choose too big a cylinder against the rule, whereas in the opposite condition, i. e. when his hyperopia is undercorrected or his myopia overcorrected, he tends to choose too big a cylinder with the rule. The dilemma does not occur to the same extent when the axis of the cylinder is oblique and may be entirely absent when it is at 45 or 135. One of the factors responsible for its occurrence is that blurred letters are more easily recognizable when their vertical parts are relatively in focus than when their horizontal parts are. The occurrence of these defects emphasizes the need for accurate retinoscopy. The duochrome letter test is of great assistance in keeping the astigmatism mixed. The author checks up on it now and then as he increases or diminishes the cylindric correction during the course of the cross cylinder test, adding plus or minus spheres as required to make the letters on the red and green equally defined. The black and white letters are then used for comparison of the two positions of the cross cylinder.

The article is illustrated.

W. ZENTMAYER.

Retina and Optic Nerve

A Case of "Hole" at Macula Due to Looking at the Sun. C. A. Pittar, Brit. J. Ophth. **27**: 36 (Jan.) 1943.

The patient was a seaman aged 26 years who complained of defective vision in the right eye of about ten months' duration. The visual acuity was 2/60. There was a small corneal nebula.

The fundus examination revealed a hole at the macula with the typical punched-out appearance. There was an absolute central scotoma of a diameter of about 4 degrees. The records of the examination made at the hospital where the patient was first treated mentioned edema of the retina at the macula with pigmentary changes.

The patient stated that enemy planes had a habit of flying out of the sun and that on several occasions he had looked at the sun, but there was no clear history of one specific occasion after which the visual defect occurred.

W. Zentmayer.

Trachoma

Local Use of Sulfanilamide for Trachoma. H. F. Morate, Semana méd. **49**: 1059 (Oct. 29) 1942.

Morate resorted to various sulfonamide compounds in the treatment of trachoma in 18 children and adults. The drugs were well tolerated by the conjunctiva and the cornea. The subjective symptoms rapidly disappeared, regardless of the clinical form and the duration of the disease. The therapy is simple, economic, painless, clean and hygienic. It resulted in a cure in 33 per cent of the patients and in amelioration of the symptoms and prevention of complications in the rest.

J. A. M. A. (W. Zentmayer).

Tumors

Haemangioma of the Orbit, Removed by Operation. T. Crawford, E. F. King and H. W. Rodgers, Brit. J. Ophth. **27**: 61 (Feb.) 1943.

A soldier aged 30, stationed in Hong Kong, had slowly increasing exophthalmos of the right eye, accompanied by numbness and neuralgic pains. Two years later, on his return to the United Kingdom, there was well marked proptosis without symptoms other than a contraction of the field of vision. The roentgen examination gave negative results. A dark red tumor of irregular shape was removed from the muscle cone by means of an osteoplastic resection of the outer wall of the orbit. Injury to the nerve supply to the iris, ciliary body and lateral rectus muscle resulted, but the visual field, visual acuity and position of the eyeball were normal.

The tumor was a mixed capillary and cavernous hemangioma arising presumably from the blood vessels lying among the orbital fatty tissues.

The article is illustrated.

W. Zentmayer.

Society Transactions

EDITED BY DR. W. L. BENEDICT

NEW YORK ACADEMY OF MEDICINE, SECTION OF OPHTHALMOLOGY

DANIEL B. KIRBY, M.D., *Chairman*

R. TOWNLEY PATON, M.D., *Secretary*

April 19, 1943

Peripheral Retinal Holes Without Detachment. DR. ARNOLD KNAPP.

This article will be published in full in a later issue of the ARCHIVES.

Case of Chronic Mercurialism with a Colored Reflex from the Anterior Lens Capsule. DR. WALTER S. ATKINSON.

The purpose of this communication is to report a brownish reflex from the anterior capsule of the lens which occurs in persons with chronic mercurialism and in those who have worked for a long time with mercury or in an atmosphere containing it. It is a rather homogeneous reflex seen well with a slit lamp containing a low power objective. It varies from a light brownish gray to a deep rose-brown, and the color is deeper in the pupillary area. When the reflex is marked, the lenses appear dull gray when examined with oblique illumination. With the ophthalmoscope they look perfectly clear. The apparent haziness of the anterior capsule and the colored reflex do not interfere with vision.

The colored reflex has been observed in 37 persons, 14 of whom exhibited symptoms of chronic mercurialism. This reflex and a fine intention tremor were the most constant sign and symptom of chronic mercurialism. The colored reflex is suggested as a permanent and probably early diagnostic sign of chronic mercurialism.

A case was reported briefly.

DISCUSSION

DR. MAYNARD C. WHEELER: I should like to congratulate Dr. Atkinson on what I consider an original piece of work. It is not easy to find something completely new in the field of ophthalmology, and few persons have the ability to appreciate the significance of a new finding and to work it up as beautifully as Dr. Atkinson has done. I have seen 2 of the patients and can only say that the picture as he has described it is definite with the slit lamp. The observation of this reflex is a good object lesson to ophthalmologists to use the slit lamp more frequently.

DR. CLYDE E. MCDANNALD: Was a biospectroscopic examination made of the skin? I do not know whether this method is still used, but a few years ago it was extensively employed for the detection of metal retention in the body.

DR. WALTER E. ATKINSON: I should like to thank Dr. Wheeler and Dr. McDannald for their discussion of my paper. The skin was not examined by the method Dr. McDannald mentioned.

Combined Intracranial and Orbital Operation for Retinoblastoma. DR. BRONSON S. RAY and DR. JOHN M. MCLEAN.

This article will be published in full in a later issue of the ARCHIVES.

Inflammation Following Perforating Injuries. Dr. Georgiana Theobald.

Inflammatory conditions following a perforating injury of the eye depend on the severity of the injury, the allergic sensitivity of the tissues and their tolerance to injury and infection. The ultimate diagnosis is dependent both on the clinical and on the microscopic picture. Because the anterior part of the eye is most frequently injured, the iris and ciliary body are especially involved. The inflammation may be limited to them, or the tissues in the posterior half of the globe may become affected.

Acute or purulent endophthalmitis occurs shortly after perforation. It involves the iris and the tissues lining the vitreous cavity. It is characterized by the formation of pus, which is found bathing these tissues; abscess may form in the vitreous. The choroid is only slightly involved.

Chronic septic endophthalmitis is delayed in its onset—usually until after the wound is healed; there is no real suppuration, although abscesses may be formed. Clinically the eye may be pale, and attention may be drawn to the condition when the patient complains of impaired vision.

In post-traumatic chronic infiltrating iritis (iritis serosa), the same tissues are involved as in endophthalmitis, but they do not exude pus; they are infiltrated by mononuclear cells. This is the condition most often clinically confused with sympathetic ophthalmia. The aqueous becomes turbid, and precipitates form on the posterior surface of the cornea.

Panophthalmitis may be purulent or septic, and, of course, all coats of the eye are involved.

In sympathetic ophthalmia the uveal tract becomes infiltrated and thickened by granulation tissue. The granulations attack the uvea in such a characteristic manner that the pathologic diagnosis is seldom difficult when the history is known. The low incidence of sympathetic ophthalmia is attributed to early enucleation of severely injured eyes and to the use of vaccines and foreign proteins.

Global wounds and ruptures heal by proliferation of fibroblasts derived from the episclera and uveal tract.

Unusual Manifestations of Malignant Melanoma of Uveal Tract. Dr. Algernon B. Reese.

1. A juxtapapillary tumor may extend around the termination of the lamina vitrea and protrude toward the interior of the eye over the site of the optic disk and therefore give a clinical picture resembling that of a lesion arising from the disk instead of from the area around the disk. (Clinical and microscopic illustrations were shown.)

2. A diffuse growth may involve the entire uveal tract almost uniformly with no actual localized tumor mass. Such a lesion is perhaps more prone to appear in cases of congenital melanosis oculi. The tumor may only be diffuse, or it may be diffuse with the usual localized globular malignant melanoma arising at some site in the uveal tract. In 25 per cent of the cases of melanosis oculi reported in the literature malignant melanoma of the uveal tract developed. The growth may be diffuse in the choroid alone, and the retina may then be adherent to the underlying and involved choroid, or it may become detached. Also, the growth may be diffuse only in the iris and ciliary body; this type includes the ring type of melanoma. (Clinical and microscopic illustrations were shown.)

3. When a malignant melanoma grows in the usual form of a globular mass the retina may be pushed ahead of the growth and cover its surface. In some instances the retina is adherent to the surface of the tumor and there are pigmentary changes secondary to proliferation of the pigment epithelium; in other instances the retina is detached over the growth, and in rarer instances the growth extends through the retina. (A clinical and microscopic illustration of the last-mentioned unusual manifestation was shown.)

4. Congenital benign melanomas of the uveal tract and, in particular, of the choroid are fairly common (affecting 1 per cent of all eyes). Malignant melanomas seem to develop from benign melanomas. The origin may be spontaneous or precipitated by old pathologic change. That is, a benign melanoma may be stimulated to become malignant by old inflammatory processes. This seems to explain the not infrequent development of a malignant melanoma in an eye blind from an old pathologic process. Evidence that malignant melanomas arise from congenital benign melanomas is furnished by the examination of malignant melanomas in which more or less benign areas can be seen around the base of the tumor. (Illustrations were shown.)

5. Types of growth manifested by malignant melanomas of the uveal tract are as follows:

(*a*) Implantation growths are common in cases of retinoblastoma but are relatively rare in cases of malignant melanoma. The development of the ring type of melanoma is probably dependent in a large measure on implantation growths around the angle. (Illustrations were shown.)

(*b*) Local metastases in the eye apparently occur in rare instances when the malignant melanoma cells pass through blood or lymph channels to other sites in the same eye. (An illustration was shown.)

(*c*) The tumor may grow by direct extension and invasion of the surrounding tissues. (An illustration was shown.)

(*d*) Multiple melanomas of independent origin in a single eye are perhaps more common than is generally believed.

Examples are (1) a tumor primary in the iris and/or ciliary body with secondary foci in the choroid; (2) a tumor primary in the choroid with secondary manifestations elsewhere in the choroid, and (3) a tumor primary in the choroid with secondary manifestations in the iris. The secondary lesions have certain characteristics which are different from those of the primary site. (These were enumerated and illustrated, and the clinical significance of an iris lesion when a primary growth is suspected in the choroid was described and illustrated.)

Subconjunctival Dislocation of Lens with Sympathetic Ophthalmia. DR. CHARLES A. PERERA.

Sympathetic ophthalmia, described over a hundred years ago by MacKenzie, is a serious disease of the eyes, and fortunately very rare. It occurs in about 0.1 to 0.15 per cent of clinic patients and in about 90 per cent of the instances follows a perforating wound of the eyeball or an intraocular operation. A survey of the literature by R. Irvine in 1940 showed that sympathetic ophthalmia followed a perforating wound of the eyeball in 1 or 2 per cent of the cases. Statistics recorded by many authors show that in 25 to 40 per cent of cases it is associated with an operation on the eyeball. The disease occurs at all ages and predominantly in males. It has been described in cases of necrotic malignant melanoma of the uveal tract (with and without perforation of the involved globe), following perforating ulcers of the cornea and as an aftermath of contusion of the eyeball with subconjunctival rupture of the globe. The few examples of sympathetic ophthalmia following contusion without rupture of the eyeball are open to doubt. Andersson in 1938 reported a case supposedly of this condition in a child, only to find a tiny perforating wound of the sclera, choroid and retina in a study of serial microscopic sections of the enucleated eye. Exhaustive studies of sympathetic ophthalmia in recent years have been made by E. Fuchs, Theobald, A. Fuchs, Joy, Woods, Samuels, Trowbridge, Gördüren and Sohr and R. Irvine. The two main etiologic theories of sympathetic ophthalmia are (1) virus infection and (2) allergy, probably to uveal pigment. Tuberculosis as a cause is becoming less tenable.

Sympathetic ophthalmia following rupture of the eyeball with subconjunctival dislocation of the lens has rarely been recorded. In each case it is impossible to eliminate the possibility of a conjunctival tear at the time of the injury.

REPORT OF A CASE

E. L., a 70 year old white woman, a widow, was seen in November 1941 in consultation concerning a "growth" of the left eye. This eye had suffered from poor vision and recurring intraocular hemorrhages following keratitis at the age of 18. The onset of the patient's present illness followed a fall eight weeks before I first examined her. She stated that she struck her left temple and that a severe hemorrhage appeared in her left eye, followed by a "growth." Four weeks later the vision of her right eye became obscured by "cobwebs," and she consulted a local oculist, who prescribed atropine sulfate drops and hot compresses and advised the removal of her seven remaining teeth. The extraction of the teeth had no effect on her eyes, and the vision of her right eye failed rapidly.

Examination of her eyes eight weeks after her fall showed a soft right eye, with a plastic exudate in the anterior chamber, many posterior synechias, incipient cataract, a cloudy vitreous and vision equal to perception of hand movements. The left eye showed a central corneal opacity, a projecting mass of inflamed prolapsed iris and uveal tissue beneath the bulbar conjunctiva in the lower nasal quadrant, a yellowish rounded subconjunctival mass superior to the prolapsed iris, normal intraocular pressure and vision equal to light perception. The patient was admitted to the Institute of Ophthalmology of Presbyterian Hospital with a diagnosis of subconjunctival dislocation of the lens and prolapse of the iris of the left eye and probable sympathetic ophthalmia. Dr. A. B. Reese examined her and agreed with this diagnosis. Enucleation of the left eye was performed nine weeks after the alleged injury. My study of microscopic sections of the left globe resulted in the following pathologic diagnoses: (1) indirect rupture of the globe, (2) luxation of the lens subconjunctivally, (3) aniridia, (4) sympathetic ophthalmia following injuries and (5) corneal scars. Healing of the socket was uneventful. The right eyeball has gone on to degeneration, discoloration of the iris, dense cataract and faulty light projection.

Book Reviews

Dictionary of Bio-Chemistry and Related Subjects. Editor in chief, William Marias Malisoff. Price, $7.50. Pp. 579. New York: Philosophical Library, Inc., 1943.

This book according to its editor in chief is "a pioneering effort . . . combining a mere alphabetical glossary with something resembling an encyclopedia . . . designed for readers of biochemical literature." The reviewer agrees with the statement that the book is "experimental." It contains too much antiquated and false information to enumerate in a short review. The encyclopedic parts to a large extent lack objectivity; the glossary is lacking in information.

A reader with ophthalmologic interests will find under the heading visual purple: "Rhodopsin: reddish purple pigment of retinal rods, see also Eye, Biochemistry of." In the chapter referred to, apparently based entirely on Krause's book (1934), he will find only this information on visual purple: "The role of visual purple in the rod-shaped cells of the retina is unique."

KARL MEYER.